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UTILITY
PATENT APPLICATION

on

PARA-SULFONYL SUBSTITUTED PHENYL COMPOUNDS AS MODULATORS OF PPARS

by

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/461,577 filed April 7, 2003.

FIELD OF THE INVENTION

The present invention is in the field of medicinal chemistry. More specifically, the present invention relates to novel para-sulfonyl substituted phenyl derivatives and methods for treating various diseases by modulation of nuclear receptor mediated processes using these compounds, and in particular processes mediated by peroxisome proliferator activated receptors (PPARs).

BACKGROUND OF THE INVENTION

Peroxisome proliferators are a structurally diverse group of compounds which, when administered to mammals, elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes required for the β-oxidation cycle (Lazarow and Fujiki, *Ann. Rev. Cell Biol.* 1:489-530 (1985); Vamecq and Draye, *Essays Biochem.* 24:1115-225 (1989); and Nelali et al., *Cancer Res.* 48:5316-5324 (1988)). Compounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models. Compounds included in this group are the fibrate class of hypolipidermic drugs, herbicides, and phthalate plasticizers (Reddy and Lalwani, *Crit. Rev. Toxicol.* 12:1-58 (1983)). Peroxisome proliferation can also be elicited by dietary or physiological factors such as a high-fat diet and cold acclimatization.

Biological processes modulated by PPAR are those modulated by receptors, or receptor combinations, which are responsive to the PPAR receptor ligands. These processes include, for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinemia (resulting from, for example, abnormal pancreatic beta cell function, insulin secreting tumors and/or autoimmune hypoglycemia due to

autoantibodies to insulin, the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which lead to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, and adipocyte differentiation.

Subtypes of PPAR include PPAR-alpha, PPAR-delta (also known as NUC1, PPAR-beta, and FAAR) and two isoforms of PPAR-gamma. These PPARs can regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements (PPRE). To date, PPRE's have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs play a pivotal role in the adipogenic signaling cascade and lipid homeostasis (H. Keller and W. Wahli, *Trends Endoodn. Met.* 291-296, 4 (1993)).

Insight into the mechanism whereby peroxisome proliferators exert their pleiotropic effects was provided by the identification of a member of the nuclear hormone receptor superfamily activated by these chemicals (Isseman and Green, Nature 347-645-650 (1990)). The receptor, termed PPAR-alpha (or alternatively, PPARα), was subsequently shown to be activated by a variety of medium and long-chain fatty acids and to stimulate expression of the genes encoding rat acyl-CoA oxidase and hydratase-dehydrogenase (enzymes required for peroxisomal β-oxidation), as well as rabbit cytochrome P450 4A6, a fatty acid ω-hydroxylase (Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657 (1992); Tugwood et al., EMBO J 11:433-439 (1992); Bardot et al., Biochem. Biophys. Res. Comm. 192:37-45 (1993); Muerhoff et al., J Biol. Chem. 267:19051-19053 (1992); and Marcus et al., Proc. Natl. Acad Sci. USA 90(12): 5723-5727 (1993).

Activators of the nuclear receptor PPAR-gamma (or alternatively, PPARγ), for example troglitazone, have been clinically shown to enhance insulin-action, to reduce serum glucose and to have small but significant effects on reducing serum triglyceride levels in patients with Type 2 diabetes. See, for example, D. E. Kelly et al., *Curr. Opin. Endocrinol. Diabetes,* 90-96, 5 (2), (1998); M. D. Johnson et al., *Ann. Pharmacother.*, 337-348, 32 (3), (1997); and M. Leutenegger et al., *Curr. Ther. Res.*, 403-416, 58 (7), (1997).

PPAR-delta (or alternatively, PPARδ) is broadly expressed in the body and has been shown to be a valuable molecular target for treatment of dyslipedimia and

other diseases. For example, in a recent study in insulin-resistant obese rhesus monkeys, a potent and selective PPAR-delta compound was shown to decrease VLDL and increase HDL in a dose response manner (Oliver et al., *Proc. Natl. Acad. Sci. U. S. A.* 98: 5305, 2001).

Because there are three isoforms of PPAR and all of them have been shown to play important roles in energy homeostasis and other important biological processes in human body and have been shown to be important molecular targets for treatment of metabolic and other diseases (see Willson, et al. J. Med. Chem. 43: 527-550 (2000)), it is desired in the art to identify compounds which are capable of selectively interacting with only one of the PPAR isoforms or compounds which are capable of interacting with multiple PPAR isoforms. Such compounds would find a wide variety of uses, such as, for example, in the treatment or prevention of obesity, for the treatment or prevention of diabetes, dyslipidemia, metabolic syndrome X and other uses.

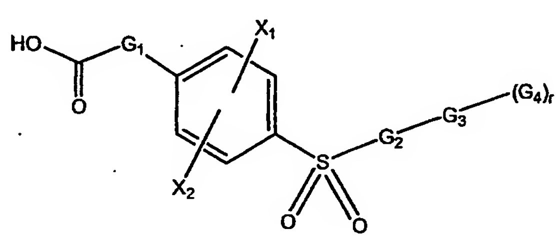
SUMMARY OF THE INVENTION

Described herein are novel para-sulfonyl substituted phenyl compounds capable of modulating the activity of human peroxisome proliferator activated receptor of the subtype delta (hPPAR–delta), and methods for utilizing such modulation to treat a disease or condition mediated or impacted by hPPAR–delta activity. Also described are pharmaceutical compositions comprising para-sulfonyl substituted phenyl derivatives that modulate the activity of hPPAR–delta. Further described are methods for making and producing novel para-sulfonyl substituted phenyl derivatives. Also described are the therapeutic or prophylactic use of novel para-sulfonyl substituted phenyl derivatives or compositions comprising them, and methods of treating metabolic disorders and conditions, by administering effective amounts of such compounds.

One embodiment of the present invention are novel sulfonyl-derived compounds, including pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, pharmaceutically acceptable solvates, and pharmaceutically acceptable salts thereof. In another aspect of the present invention is the synthesis of such sulfonyl-derived compounds, and pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, pharmaceutically acceptable solvates or pharmaceutically acceptable salts thereof. In yet another aspect of the present

invention are pharmaceutical compositions of such para-substituted phenyl compounds, including pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, pharmaceutically acceptable solvates or pharmaceutically acceptable salts thereof. In another aspect of the present invention are sulfonyl-derived compounds that can modulate the activity of hPPAR-delta in vitro and/or in vivo. In yet another aspect of the present invention are sulfonyl-derived compounds that can selectively modulate the activity of hPPAR-delta. In yet another aspect are methods for modulating hPPAR-delta comprising contacting the hPPAR-delta -modulating compounds, or pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, pharmaceutically acceptable solvates or pharmaceutically acceptable salts thereof, described herein, with hPPAR-delta or with cells comprising hPPAR-delta. In yet another aspect are methods for treating a disease or condition in a patient comprising administering a therapeutically effective amount of a hPPAR-delta -modulating compound, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable solvate or pharmaceutically acceptable salt thereof. In yet another aspect are methods for preventing a condition or disease in a patient comprising administering a prophylactically effective amount of a hPPAR-delta -modulating compound, or a pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable solvate or pharmaceutically acceptable salt thereof.

In one aspect presented herein are compounds having the structure of Formula (I):



(I)

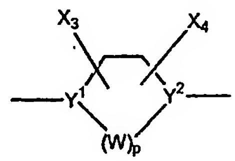
wherein:

G_1 is selected from the group consisting of $-(CR^1R^2)_n-$ and $-(CR^1R^2)_nO-$, wherein n is 1 or 2 and each R^1 and each R^2 are independently hydrogen,

C_{1-4} alkyl, C_{1-4} heteroalkyl, C_{1-4} alkoxy, and C_{1-4} perhaloalkyl or together may form a cycloalkyl, provided that R^1 and R^2 are not both H when n is 1;

X_1 and X_2 are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, cycloalkyl, halogen, perhaloalkyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, and NH_2;

G_2 is a cyclic moiety having structure



wherein Y^1 and Y^2 are each independently N or C–X_5;

X_3 and X_4 are each independently selected from the group consisting of hydrogen, alkyl, halogen, C_{1-4} perhaloalkyl, hydroxy, alkoxy, nitro, cyano, NH_2;

p is 1, 2 or 3;

W is independently selected from the group consisting of $-CX_3X_4-$, N–X_6, and a moiety which together with Y^2, forms a double bond;

X_5 is selected from the group consisting of hydrogen, alkyl, hydroxy, alkoxy, cyano, halogen, C_{1-4} perhaloalkyl and NH_2; provided further that when X_5 is alkyl, alkoxy or C_{1-4} perhaloalkyl, then such groups may be optionally ligated to G_4;

X_6 is selected from the group consisting of hydrogen, alkyl, hydroxy, and C_{1-4} perhaloalkyl, or null when forming a double bond with Y^2;

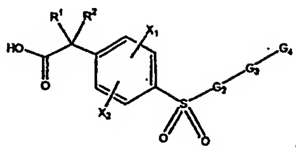
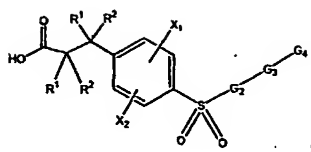
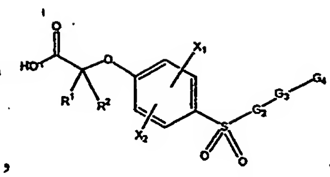
G_3 is selected from the group consisting of a bond, a double bond, $-(CR^3R^4)_m-$, $-C(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mCO-$, and $-(CR^3R^4)_mCR^3{=}CR^4-$, wherein m is 0, 1, or 2, and wherein each R^3 and each R^4 is independently H, C_{1-4} alkyl, C_{1-4} alkoxy, aryl, C_{1-4} perhaloalkyl, cyano, and nitro; and

G_4 is selected from the group consisting of optionally substituted aryl, heteroaryl, cycloalkyl, cycloheteroaryl, and cycloalkenyl; and wherein Y^2 is C–X_5, G_4 may be optionally ligated to X_5; and

r is 1 or 2;

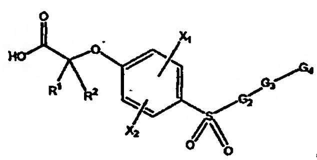
or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof.

In one embodiment of compounds having the structure of Formula (I) are compounds having a structural formula selected from the group consisting of:

, , .

In a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In yet a further embodiment, R^1 and R^2 are each methyl.

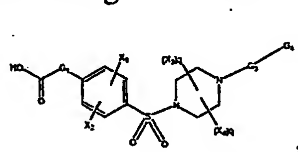
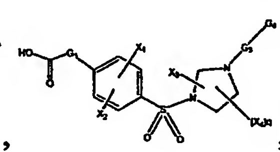
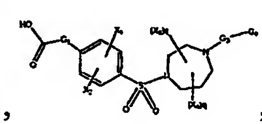
In another embodiment of compounds having the structure of Formula (I) are compounds having the structure:

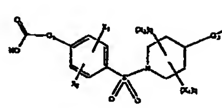
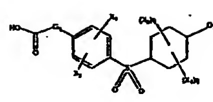
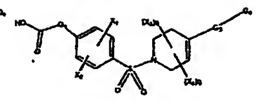
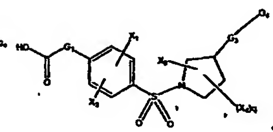
.

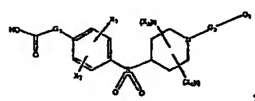
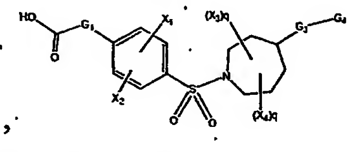
In a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In yet a further embodiment, R^1 and R^2 are each methyl. In a further embodiment, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl. In yet a further embodiment, X_1 and X_2 are each independently selected from the group consisting of hydrogen and methyl.

In another embodiment of compounds having the structure of Formula (I), X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl. In a further embodiment, X_1 and X_2 are each independently selected from the group consisting of hydrogen and methyl.

In another embodiment of compounds having the structure of Formula (I) are compounds having a structural formula selected from the group consisting of:

, , ,

,   ,

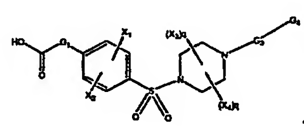
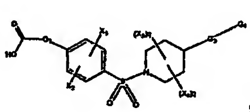
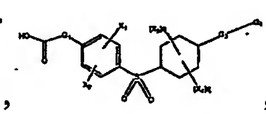
, 

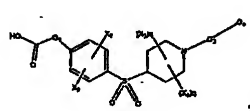
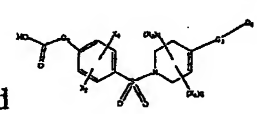
wherein q = 0, 1, or 2.

In a further embodiment, G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$. In yet a further embodiment, G_1 is $-OCR^1R^2-$. In yet a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In still a further embodiment, R^1 and R^2 are each methyl.

In an alternative embodiment of compounds having the structural formula presented above, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl. In yet a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl. In still a further embodiment, R^1 and R^2 are each methyl.

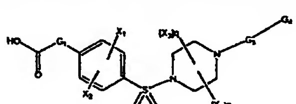
In an further embodiment of compounds having the structural formula presented above are compounds having structural formula selected from the group consisting of:

, , ,

,and 

wherein q = 0, 1, or 2.

In a further embodiment, are compounds having the structural formula:

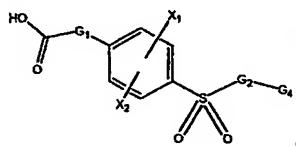
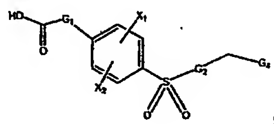
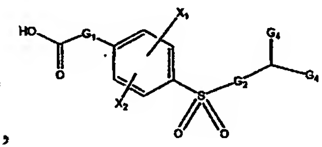
, wherein q = 0, 1, or 2.

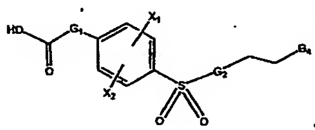
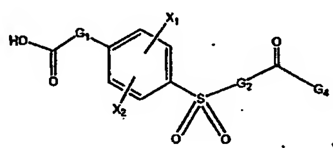
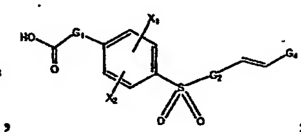
In yet a further embodiment, G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$. In still a further embodiment, G_1 is $-CR^1R^2-O-$. In yet a further embodiment, R^1 and R^2 are each independently selected from the

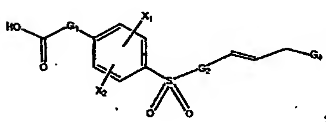
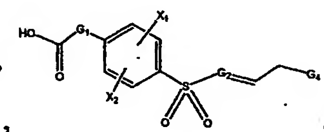
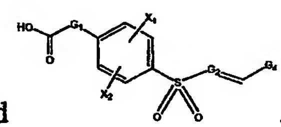
group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In still a further embodiment, R^1 and R^2 are each methyl.

In another embodiment of the compounds having the structural formula presented above, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

In another embodiment of compounds having the structure of Formula (I) are compounds having a structural formula selected from the group consisting of:

, , ,

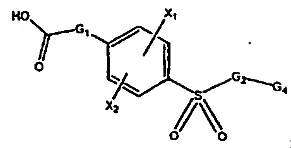
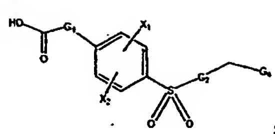
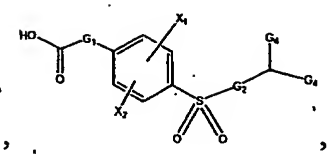
, , ,

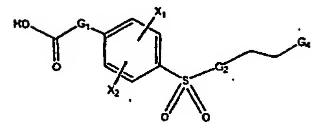
, , and .

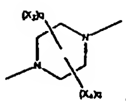
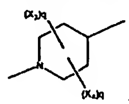
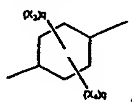
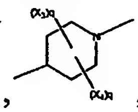
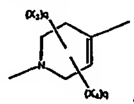
In a further embodiment, G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$. In still a further embodiment, G_1 is $-CR^1R^2-O-$. In yet another embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In still a further embodiment, R^1 and R^2 are each methyl.

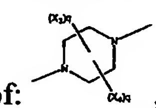
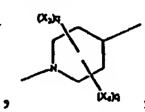
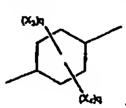
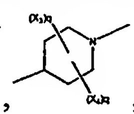
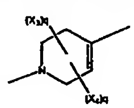
In another embodiment of the compounds having the structural formula presented above, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl. In still a further embodiment, G_1 is $-CR^1R^2-O-$. In yet another embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In still another embodiment, R^1 and R^2 are each methyl.

In another embodiment of the compounds having the structural formula presented above are compounds having the structural formula selected from the group consisting of:

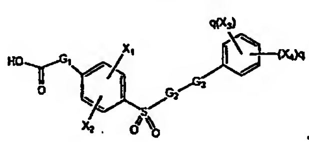
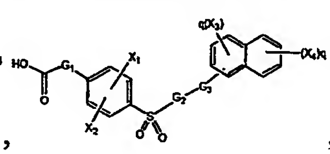
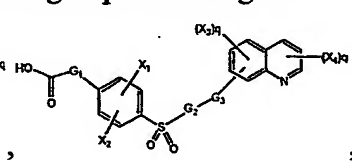
 ,  ,  , and

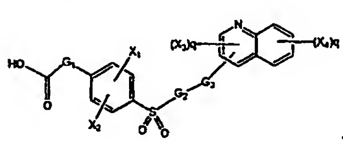
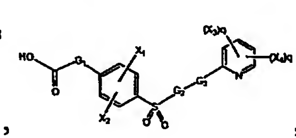
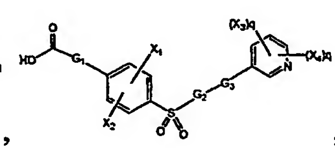
 .

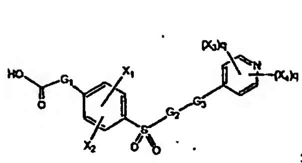
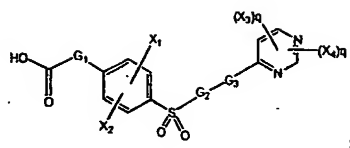
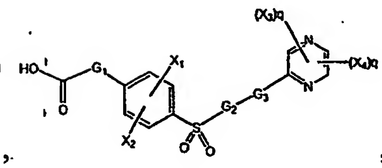
In a further embodiment, G_2 is selected from the group consisting of:  ,  ,  ,  , and  . In another embodiment, G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$. In yet another embodiment, G_1 is $-CR^1R^2-O-$. In still another embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In yet another embodiment, R^1 and R^2 are each methyl.

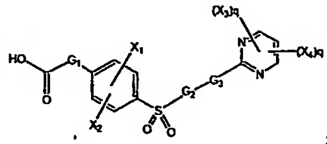
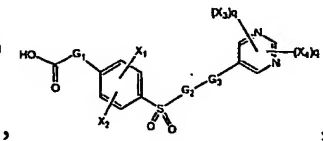
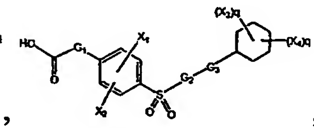
In another embodiment of the compounds having the structural formula shown above, G_2 is selected from the group consisting of:  ,  ,  ,  , and  and X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl. In yet a further embodiment, G_1 is $-CR^1R^2-O-$. In still a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In yet a further embodiment, R^1 and R^2 are each methyl.

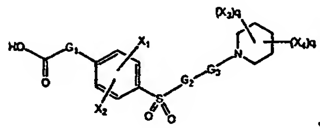
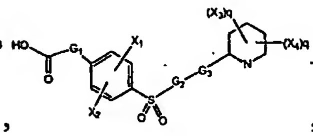
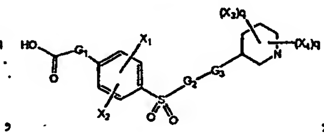
In another embodiment of compounds having the structure of Formula (I) are compounds having a structural formula selected from the group consisting of:

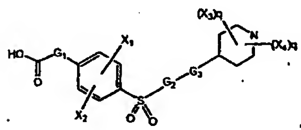
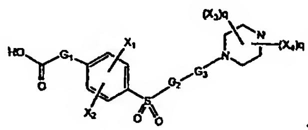
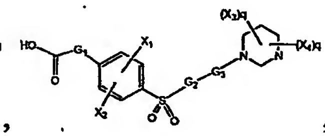
 ,  ,  ,

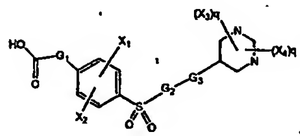
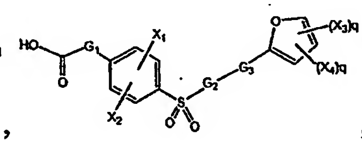
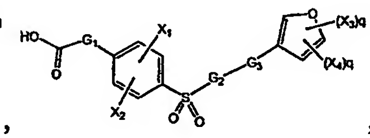
 ,  ,  ,

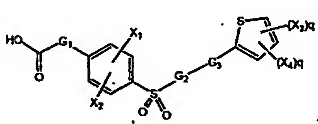
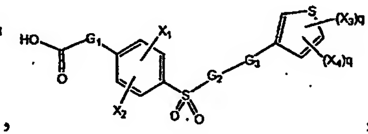
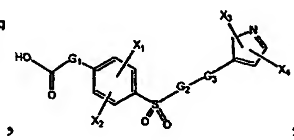
, , ,

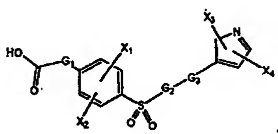
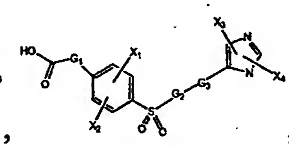
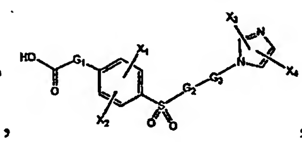
, , ,

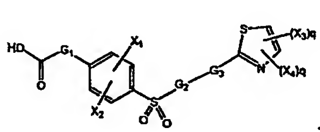
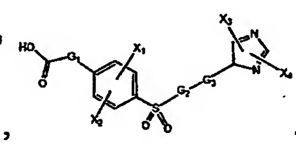
, , ,

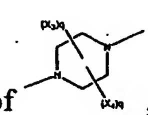
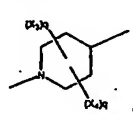
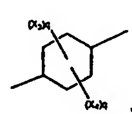
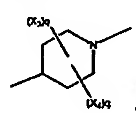
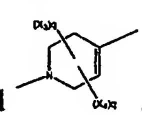
, , ,

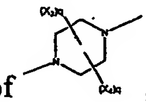
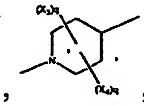
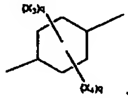
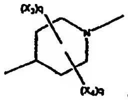
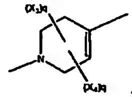
, , ,

, , ,

, , ,

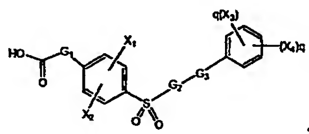
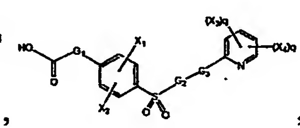
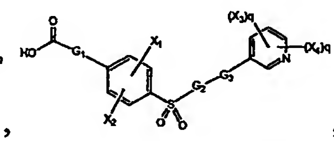
, .

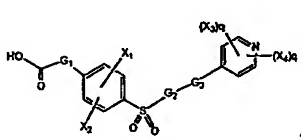
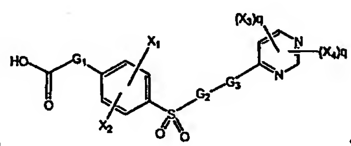
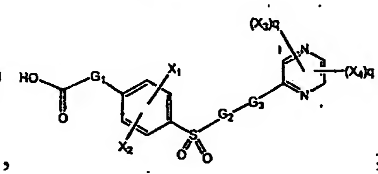
In yet a further embodiment of such compounds, G_2 is selected from the group consisting of , , , , and . In still a further embodiment, G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$. In still a further embodiment, G_1 is $-CR^1R^2-O-$. In yet a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In yet a further embodiment, R^1 and R^2 are each methyl.

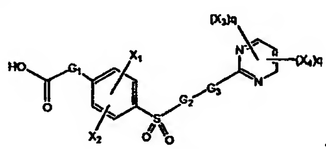
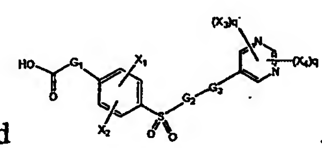
In another embodiment of compounds having the structural formulas presented above, G_2 is selected from the group consisting of  ,  ,  ,  , and  , and X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

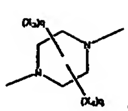
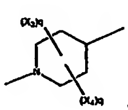
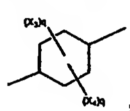
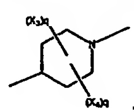
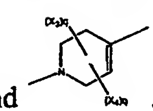
In another embodiment of compounds having the structural formulas presented above, G_3 is either a bond or $-CH_2-$.

In another embodiment of compounds having the structural formulas presented above are compounds having a structural formula selected from the group consisting of:

 ,  ,  ,

 ,  ,  ;

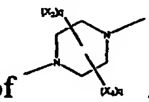
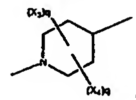
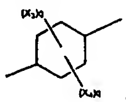
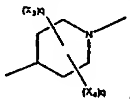
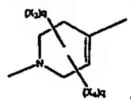
 , and  .

In a further embodiment, G_2 is selected from the group consisting of  ,  ,  ,  , and  . In still a further embodiment, G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$. In yet a further embodiment, G_1 is $-CR^1R^2-$. In still a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In yet another embodiment, R^1 and R^2 are each methyl.

In another embodiment of compounds having the structural formula presented above, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

In another embodiment of compounds having the structural formula presented above, G_3 is either a bond or $-CH_2-$.

In another embodiment of compounds having the structural formula presented above, X_3 is selected from the group consisting of halogen and C_1-C_4 perhaloalkyl; and q is 1 or 2. In yet a further embodiment, X_3 is selected from the group consisting of F, Cl and CF_3.

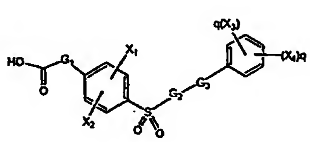
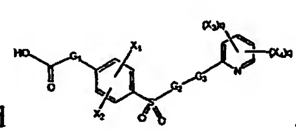
In another embodiment of compounds having the structural formula presented above, X_3 is selected from the group consisting of halogen and C_1-C_4 perhaloalkyl; and q is 1 or 2, and G_2 is selected from the group consisting of  ,  ;  ,  , and  .

In another embodiment of compounds having the structural formula presented above, X_3 is selected from the group consisting of halogen and C_1-C_4 perhaloalkyl; and q is 1 or 2; and G_1 is selected from the group consisting of $-CR^1R^2-$, $-(CR^1R^2)_2-$, and $-CR^1R^2-O-$. In a further embodiment, G_1 is $-CR^1R^2-O-$. In still a further embodiment, R^1 and R^2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl, or together may form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In still a further embodiment, R^1 and R^2 are each methyl.

In another embodiment of compounds having the structural formula presented above, X_3 is selected from the group consisting of halogen and C_1-C_4 perhaloalkyl; and q is 1 or 2 and X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

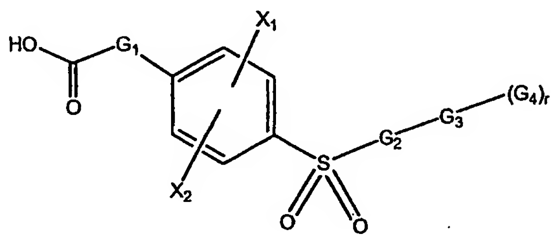
In another embodiment of compounds having the structural formula presented above, X_3 is selected from the group consisting of halogen and C_1-C_4 perhaloalkyl; and q is 1 or 2 and G_3 is either a bond or $-CH_2-$.

In another embodiment of compounds having the structural formula presented above are compounds having a structural formula selected from the group consisting of:

 and  .

In a further embodiment, X_3 is selected from the group consisting of halogen and C_1-C_4 perhaloalkyl; and q is 1 or 2. In still a further embodiment, X_3 is selected from the group consisting of F, Cl and CF_3.

In another aspect presented herein are compounds having the structure of Formula (I)



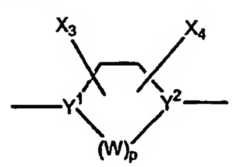
(I)

wherein:

G_1 is selected from the group consisting of $-(CR^1R^2)_n-$ and $-(CR^1R^2)_nO-$, wherein n is 1 or 2 and each R^1 and each R^2 are hydrogen;

X_1 and X_2 are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, cycloalkyl, halogen, perhaloalkyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, and NH_2;

G_2 is a cyclic moiety having structure



wherein Y^1 and Y^2 are each independently N or C–X_5;

X_3 and X_4 are each independently selected from the group consisting of hydrogen, alkyl, halogen, C_{1-4} perhaloalkyl, hydroxy, alkoxy, nitro, cyano, NH_2;

p is 1, 2 or 3;

W is independently selected from the group consisting of $-CX_3X_4-$, N–X_6, and a moiety which together with Y^2, forms a double bond;

X_5 is selected from the group consisting of hydrogen, alkyl, hydroxy, alkoxy, cyano, halogen, C_{1-4} perhaloalkyl and NH_2; provided further that when X_5 is alkyl, alkoxy or C_{1-4} perhaloalkyl, then such groups may be optionally ligated to G_4;

X_6 is selected from the group consisting of hydrogen, alkyl, hydroxy, and C_{1-4} perhaloalkyl, or null when forming a double bond with Y^2;

G_3 is selected from the group consisting of a bond, a double bond,

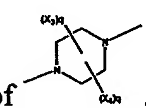
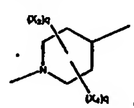
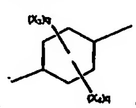
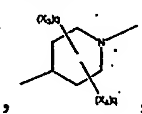
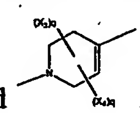
$-(CR^3R^4)_m-$, carbonyl, and $-(CR^3R^4)_mCR^3{=}CR^4-$, wherein m is 0, 1, or 2, and wherein each R^3 and each R^4 is independently H, $C_{1\text{-}4}$ alkyl, $C_{1\text{-}4}$ alkoxy, aryl, $C_{1\text{-}4}$ perhaloalkyl, cyano, and nitro; and

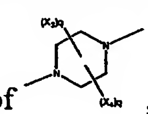
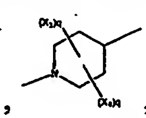
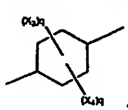
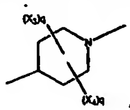
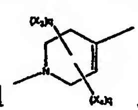
G_4 is selected from the group consisting of optionally substituted aryl, heteroaryl, cycloalkyl, cycloheteroaryl, cycloalkenyl, wherein said optional substituents are selected from the group consisting of alkyl, halogen, perhaloalkyl, perhaloalkoxy, C_1-C_4alkoxy; and wherein Y^2 is C–X_5, G_4 may be optionally ligated to X_5; and

r is 1 or 2;

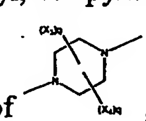
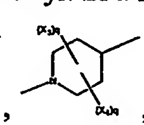
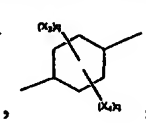
or a pharmaceutically acceptable N-oxide, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, pharmaceutically acceptable salt, pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof. For convenience, this particular aspect will be hereinafter termed Aspect 2.

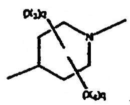
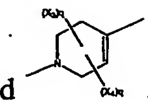
In a further embodiment of Aspect 2, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

In a further embodiment of Aspect 2, G_2 is selected from the group consisting of , , , , and . In a further embodiment, G_1 is $-CR^1R^2-$. In yet a further embodiment, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

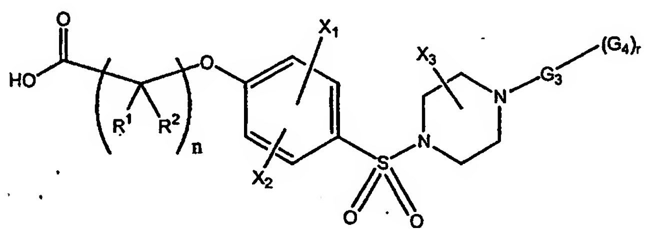
In a further embodiment of Aspect 2, G_3 is either a bond or $-CH_2-$. In a further embodiment, G_2 is selected from the group consisting of , , , , and . In a further embodiment, G_1 is $-CR^1R^2-$.

In a further embodiment of Aspect 2, G_3 is either a bond or $-CH_2-$ and X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

In a further embodiment of Aspect 2, G_4 is selected from the group consisting of an optionally substituted phenyl, pyridyl, and pyrimidyl. In a further embodiment, G_2 is selected from the group consisting of , , ,

 , and  . In a further embodiment, G_1 is $-CR^1R^2$-O-. In an alternative or further embodiment, X_1 and X_2 are each independently selected from the group consisting of hydrogen, methyl, ethyl, halogen, and propyl.

In another aspect presented herein are compounds having the structure of Formula (II)



(II)

wherein:

n is 1, 2, or 3;

each R^1 and each R^2 are independently hydrogen, C_{1-4} alkyl, C_{1-4} heteroalkyl, C_{1-4} alkoxy, and C_{1-4} perhaloalkyl or together may form a cycloalkyl, provided that R^1 and R^2 are not both H when n is 1;

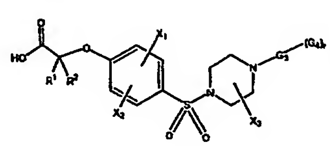
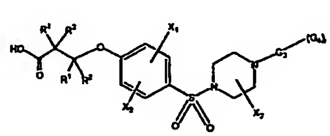
X_1, X_2, and X_3 are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, cycloalkyl, halogen, perhaloalkyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, and NH_2;

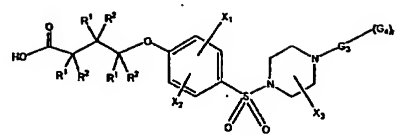
G_3 is selected from the group consisting of a bond, $-(CH_2)_m-$, carbonyl, and $-(CH_2)CH{=}CH-$, wherein m is 1 or 2; and

G_4 is selected from the group consisting of optionally substituted aryl, heteroaryl, cycloalkyl, and where r is 1 or 2;

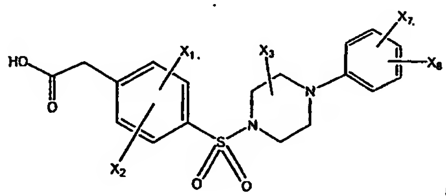
or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

In a further embodiment of compounds having the structure of Formula (II), X_1 and X_3 is hydrogen or methyl. In yet a further embodiment are compounds having a structure selected from the group consisting of

 ,  , and



In another aspect presented herein are compounds having the structure of Formula (III)



(III)

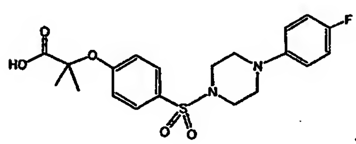
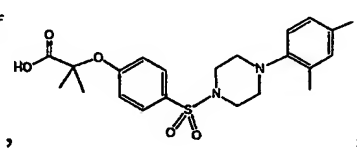
wherein:

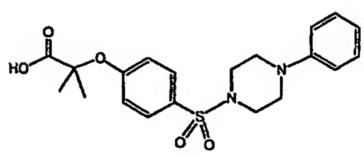
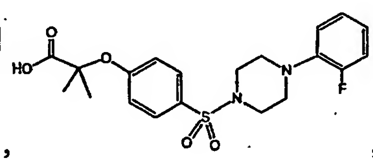
X^1, X^2, and X^3 are each independently hydrogen or C_{1-4}alkyl;

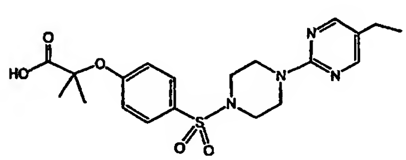
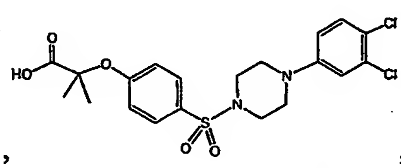
X^7 and X^8 are each independently selected from the group consisting of hydrogen, alkyl, halogen, C_{1-4} perhaloalkyl, hydroxy, alkoxy, nitro, cyano, and NH_2;

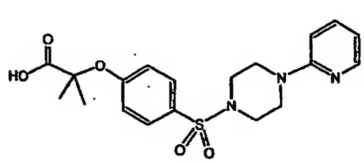
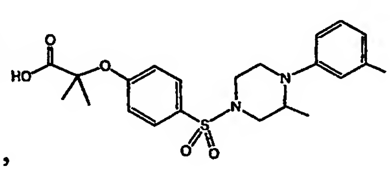
or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

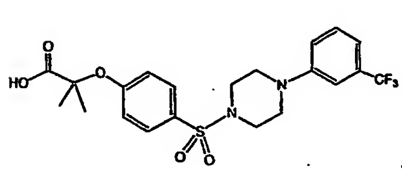
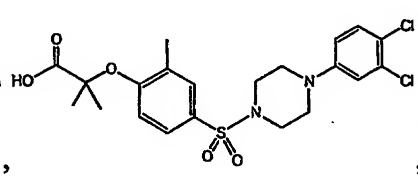
In a further embodiment of compounds having the structure of Formula (I) are compounds having a structural formula selected from the group consisting of:

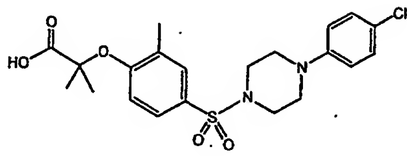
 ,  ,

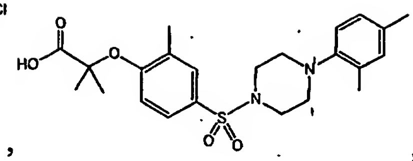
 ,  ,

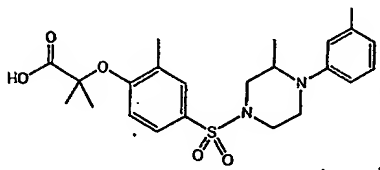
 ,  ,

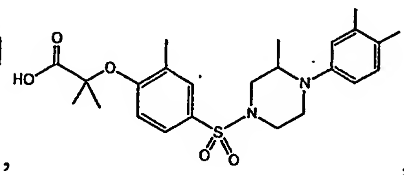
 ,  ,

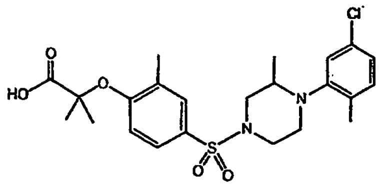
 ,  ,

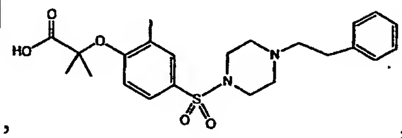
 ,

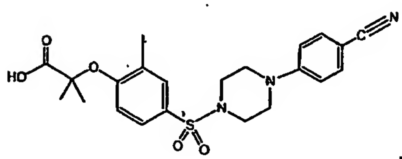
 ,

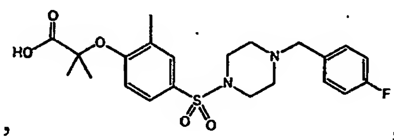
 ,

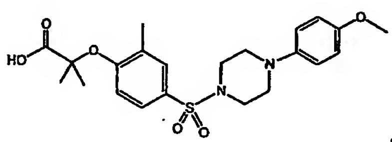
 ,

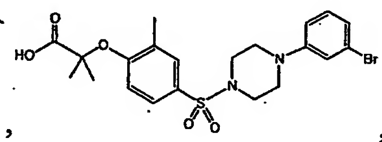
 ,

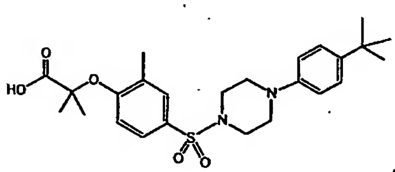
 ,

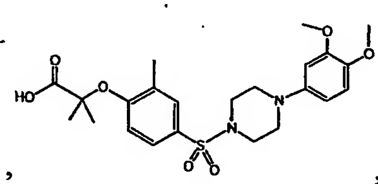
 ,

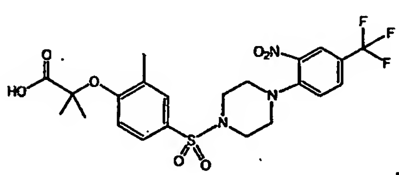
 ,

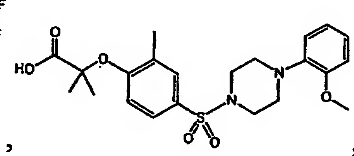
 ,

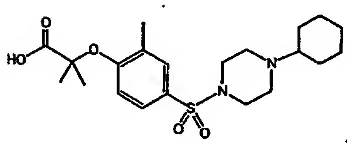
 ,

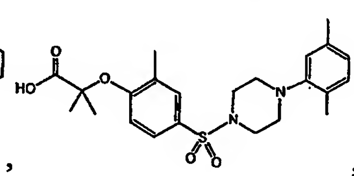
 ,

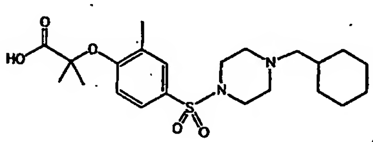
 ,

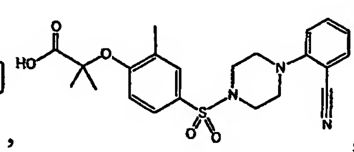
 ,

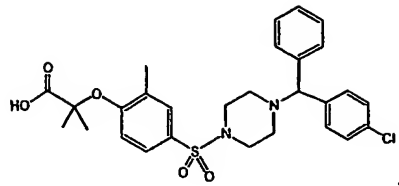
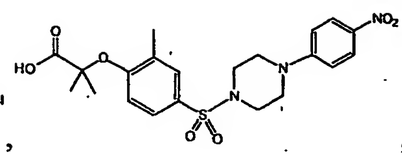
 ,

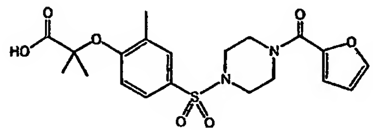
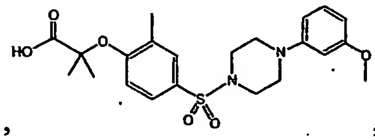
 ,

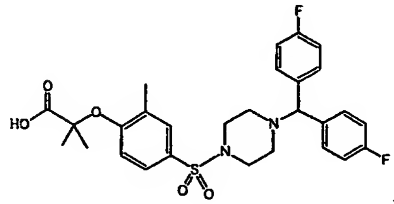
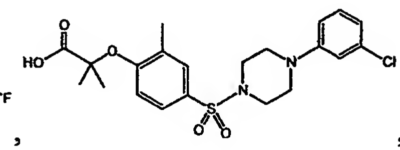
 ,

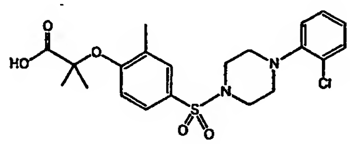
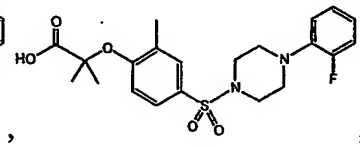
 ,

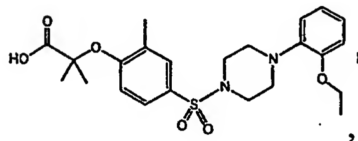
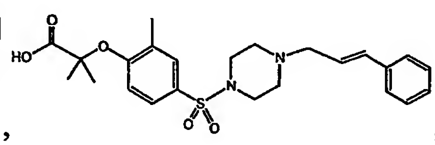
 ,

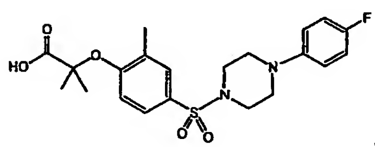
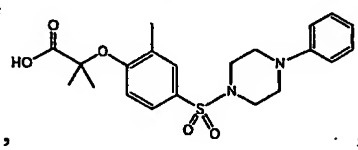
, ,

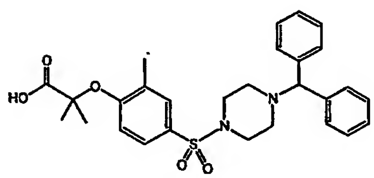
, ,

, ,

, ,

, ,

,  ,and

.

The compounds of the invention are useful in the treatment of a disease or condition ameliorated by the modulation of a hPPAR-delta. Specific diseases and conditions modulated by PPAR-delta and for which the compounds and compositions are useful include but are not limited to dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type 1 diabetes, insulin resistance hyperlipidemia, obesity, anorexia bulimia, inflammation and anorexia nervosa.

An aspect of the present invention is the use of such compounds for the treatment of a disease or condition ameliorated by the modulation of a hPPAR-delta, wherein such diseases or conditions include but are not limited to dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type 1 diabetes, insulin resistance hyperlipidemia, obesity, anorexia bulimia, inflammation and anorexia nervosa.

Another aspect of the compounds and compositions of invention is their use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the modulation of a hPPAR-delta.

Another aspect of the compounds, pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt comprising a compound having an EC_{50} value less than 1 μM as measured by a functional cell assay.

Another aspect of the invention are methods for raising HDL in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulators disclosed herein.

Another aspect of the invention is the use of a hPPAR-delta modulators disclosed herein for the manufacture of a medicament for the raising of HDL in a patient in need thereof.

Another aspect of the invention are methods for treating Type 2 diabetes, decreasing insulin resistance or lowering blood pressure in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulators disclosed herein.

Another aspect of the invention is the use of a hPPAR-delta modulator disclosed herein for the manufacture of a medicament for the treatment of Type 2 diabetes, for decreasing insulin resistance or for lowering blood pressure in a patient in need thereof.

Another aspect of the invention is the use and administration of hPPAR-delta selective modulators.

Another aspect of the invention are methods for decreasing LDLc in a subject comprising the administration of a therapeutic amount of a hPPAR delta modulator disclosed herein.

Another aspect of the invention is the use of a hPPAR-delta modulators disclosed herein for the manufacture of a medicament for decreasing LDLc in a patient in need thereof.

Another aspect of the invention are methods for shifting LDL particle size from small dense to normal dense LDL in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulators as disclosed herein.

Another aspect of the invention is the use of a hPPAR-delta modulator as disclosed herein for the manufacture of a medicament for shifting LDL particle size from small dense to normal LDL in a patient in need thereof.

Another aspect of the invention is the use of a hPPAR-delta modulator as disclosed herein for treating atherosclerotic diseases including vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulator as disclosed herein.

Another aspect of the invention is the use of a hPPAR-delta modulator disclosed herein for the manufacture of a medicament for the treatment of atherosclerotic diseases including vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease in a patient in need thereof.

Another aspect of the invention are methods for treating inflammatory diseases, including rheumatoid arthritis, asthma, osteoarthritis and autoimmune disease in a subject comprising the administration of a therapeutic amount of a hPPAR-delta modulator as disclosed herein.

Another aspect of the invention is the use of a hPPAR-delta modulator as disclosed herein for the manufacture of a medicament for the treatment of inflammatory diseases, including rheumatoid arthritis, asthma, osteoarthritis and autoimmune disease in a patient in need thereof, including those hPPAR-delta modulators which are hPPAR-delta selective modulator.

Another aspect of the invention are methods of treatment of a hPPAR-delta modulated disease or condition comprising administering a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Another aspect of the invention are methods of modulating a peroxisome proliferator-activated receptor (PPAR) function comprising contacting said PPAR

with a compound disclosed herein and monitoring a change in cell phenotype, cell proliferation, activity of said PPAR, or binding of said PPAR with a natural binding partner.

Another aspect of the invention are methods of treating a disease or condition, comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound disclosed herein to said patient, wherein said disease is selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

Another aspect of the invention is a compound described herein which modulates a peroxisome proliferator-activated receptor (PPAR) function. In another embodiment, such compounds or compositions are used in the treatment of a disease or condition ameliorated by the modulation of a PPAR. In a further embodiment, the disease or condition is dyslipidemia, metabolic syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type 1 diabetes, insulin resistance hyperlipidemia, obesity, anorexia bulimia, inflammation and anorexia nervosa. In a further embodiment of any of the prior compounds or compositions described in this paragraph, the PPAR is selected from the group consisting of PPARα, PPARδ, and PPARγ.

Another aspect of the invention is a compound described herein which modulates a peroxisome proliferator-activated receptor (PPAR) function for use in the manufacture of a medicament for the prevention or treatment of disease or condition ameliorated by the modulation of a PPAR. In a further embodiment, the PPAR is selected from the group consisting of PPARα, PPARδ, and PPARγ.

DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses that phenyl moieties substituted with an acid or ester moiety disposed para to a sulfonyl moiety can modulate at least one peroxisome proliferator-activated receptor (PPAR) function, and can confer additionally selective activation of hPPAR-delta. Compounds described herein may be activating both PPAR-delta and PPAR-gamma or PPAR-alpha and PPAR-delta, or

all three PPAR subtypes, or selectively activating predominantly hPPAR-gamma, hPPAR-alpha or hPPAR-delta.

The present invention relates to a method of modulating at least one peroxisome proliferator-activated receptor (PPAR) function comprising the step of contacting the PPAR with a compound of Formula I, as described herein. The change in cell phenotype, cell proliferation, activity of the PPAR, expression of the PPAR or binding of the PPAR with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

The present invention describes methods of treating a disease comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Formula I, as described herein, to a patient. Thus, in certain embodiments, the disease to be treated by the methods of the present invention is selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

CHEMICAL TERMINOLOGY

An "acetyl" group refers to a $-C(=O)CH_3$, group.

The term "acyl" includes alkyl, aryl, or heteroaryl substituents attached to a compound via a carbonyl functionality (e.g., -C(O)-alkyl, -C(O)-aryl, etc.).

An "alkoxy" group refers to a RO- group, where R is as defined herein.

An "alkoxyalkoxy" group refers to a ROR'O- group, where R is as defined herein.

An "alkoxyalkyl" group refers to a R'OR- group, where R and R' are as defined herein.

As used herein, the term "alkyl" refers to an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting

of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

The "alkyl" moiety may have 1 to 40 carbon atoms (whenever it appears herein, a numerical range such as "1 to 40" refers to each integer in the given range; *e.g.*, "1 to 40 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 40 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may be a "medium alkyl" having 1 to 20 carbon atoms. The alkyl group could also be a "lower alkyl" having 1 to 5 carbon atoms. The alkyl group of the compounds of the invention may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. An alkyl group may be optionally substituted.

The term "alkylamino" refers to the -NRR' group, where R and R' are as defined herein. R and R', taken together, can optionally form a cyclic ring system.

The term "alkylene" refers to an alkyl group that is substituted at two ends (i.e., a diradical). Thus, methylene ($-CH_2-$) ethylene ($-CH_2CH_2-$), and propylene ($-CH_2CH_2CH_2-$) are examples of alkylene groups. Similarly, "alkenylene" and "alkynylene" groups refer to diradical alkene and alkyne moieties, respectively. An alkylene group may be optionally substituted.

An "amide" is a chemical moiety with formula -C(O)NHR or -NHC(O)R, where R is optionally substituted and is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). An amide may be an amino acid or a peptide molecule attached to a molecule of the present invention, thereby forming a prodrug. Any amine, hydroxy, or carboxyl side chain on the compounds of the present invention can be amidified. The procedures and specific groups to be used to achieve makes such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis,

3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

A "C-amido" group refers to a -C(=O)-NR_2 group with R as defined herein.

An "N-amido" group refers to a RC(=O)NH- group, with R as defined herein.

The term "aromatic" or "aryl" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups. The term "carbocyclic" refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon. An aromatic or aryl group may be optionally substituted.

An "O-carbamyl" group refers to a -OC(=O)-NR_2 group-with R as defined herein.

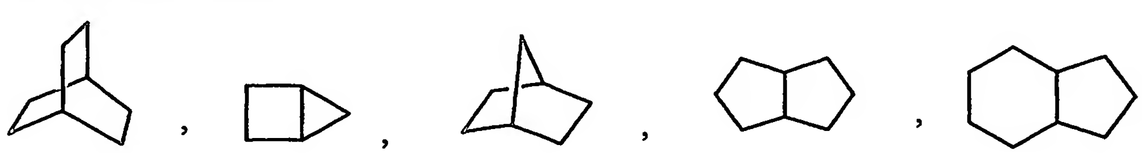
An "N-carbamyl" group refers to a ROC(=O)NH- group, with R as defined herein.

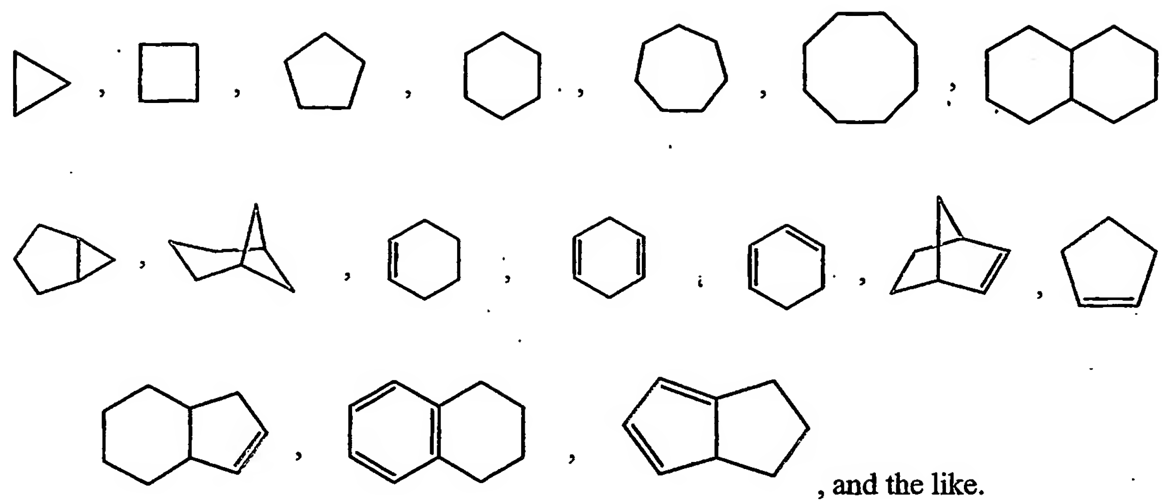
An "O-carboxy" group refers to a RC(=O)O- group, where R is as defined herein.

A "C-carboxy" group refers to a -C(=O)OR groups where R is as defined herein.

A "cyano" group refers to a -CN group.

The term "cycloalkyl" refers to a monocyclic or polycyclic radical which contains only carbon and hydrogen, and may be saturated, partially unsaturated, or fully unsaturated. A cycloalkyl group may be optionally substituted. Preferred cycloalkyl groups include groups having from three to twelve ring atoms, more preferably from 5 to 10 ring atoms. Illustrative examples of cycloalkyl groups include the following moieties:





, and the like.

The term "ester" refers to a chemical moiety with formula -COOR, where R is optionally substituted and is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). Any amine, hydroxy, or carboxyl side chain on the compounds of the present invention can be esterified. The procedures and specific groups to be used to achieve makes such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

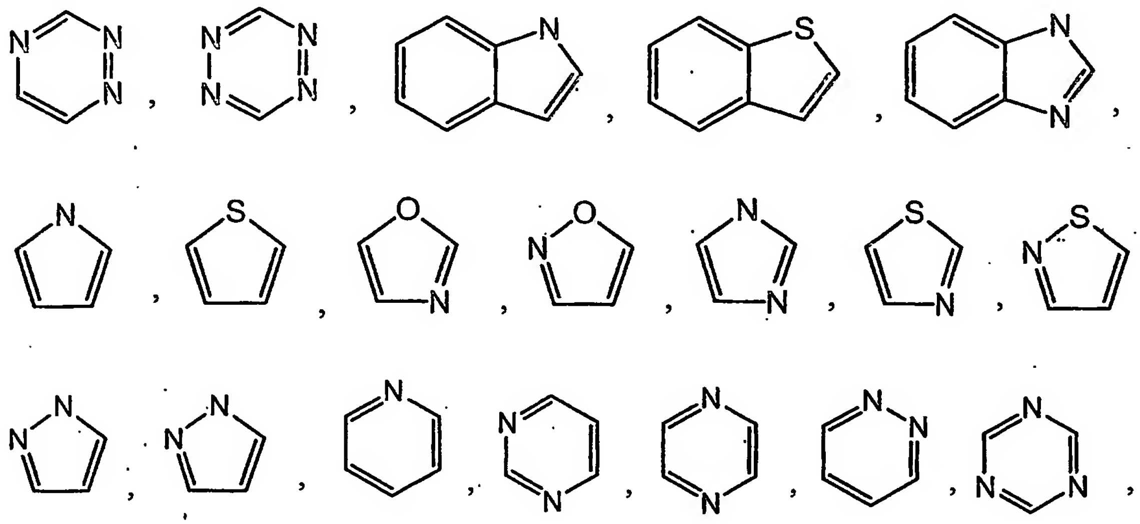
The term "halo" or, alternatively, "halogen" means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

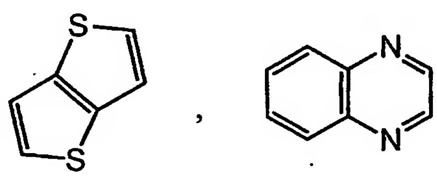
The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures, that are substituted with one or more halo groups or with combinations thereof. The terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

The terms "heteroalkyl" "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other that carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof.

The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. A heteroaryl group may be optionally substituted. An N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least

one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. Illustrative examples of aryl groups include the following moieties:

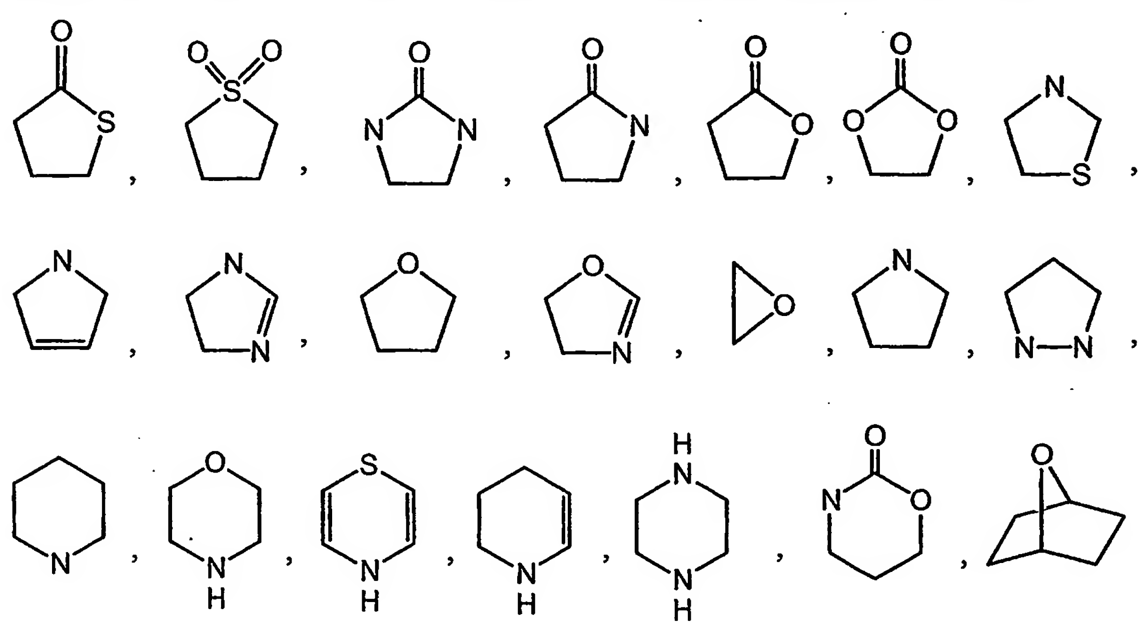


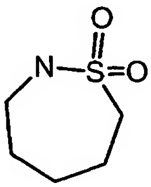
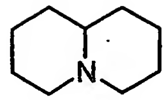
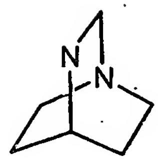
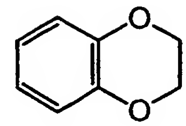
 and the like.

The term "heterocycle" refers to heteroaromatic and heteroalicyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4-membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl,

dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl or imidazol-3-yl (both N-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. A heterocycle group may be optionally substituted.

A "heteroalicyclic" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups include:



, , ,  and the like.

The term "membered ring" can embrace any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, pyridine, pyran and thiopyran are 6-membered rings and cyclopentyl, pyrrole, furan, and thiophene are 5-membered rings.

An "isocyanato" group refers to a -NCO group.

An "isothiocyanato" group refers to a -NCS group.

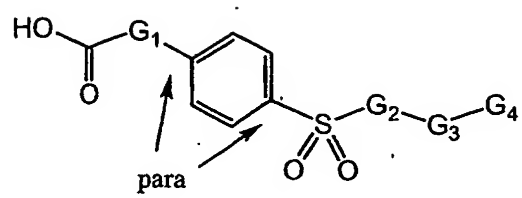
A "mercaptoalkyl" group refers to a R'SR- group, where R and R' are as defined herein.

A "mercaptomercaptyl" group refers to a RSR'S- group, where R is as defined herein.

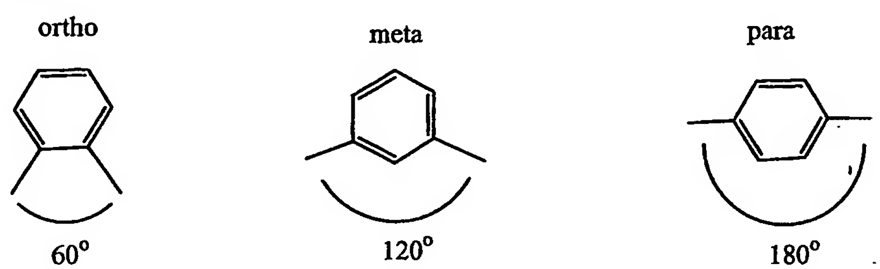
A "mercaptyl" group refers to a RS- group, where R is as defined herein.

The terms "nucleophile" and "electrophile" as used herein have their usual meanings familiar to synthetic and/or physical organic chemistry. Carbon electrophiles typically comprise one or more alkyl, alkenyl, alkynyl or aromatic (sp^3, sp^2, or sp hybridized) carbon atoms substituted with any atom or group having a Pauling electronegativity greater than that of carbon itself. Examples of carbon electrophiles include but are not limited to carbonyls (aldehydes, ketones, esters, amides), oximes, hydrazones, epoxides, aziridines, alkyl-, alkenyl-, and aryl halides, acyls, sulfonates (aryl, alkyl and the like). Other examples of carbon electrophiles include unsaturated carbon atoms electronically conjugated with electron withdrawing groups, examples being the 6-carbon in a alpha-unsaturated ketones or carbon atoms in fluorine substituted aryl groups. Methods of generating carbon electrophiles, especially in ways which yield precisely controlled products, are known to those skilled in the art of organic synthesis.

The term "para" and "para-substituted" as used herein refers to the 1,4-disposition of substituent moieties on a phenyl or other aromatic ring. For example, para-substituted phenyl derivatives bearing both an acid group and a sulfonyl group linked the same phenyl moiety may have a para disposition:



The relative dispositions of aromatic substituents (ortho, meta, and para) imparts distinctive chemistry for such stereoisomers and is well recognized within the field of aromatic chemistry. Para- and meta- substitutional patterns project the two substituents into different orientations. Ortho-disposed substituents are oriented at 60° with respect to one another; meta-disposed substituents are oriented at 120° with respect to one another; para-disposed substituents are oriented at 180° with respect to one another.



Relative dispositions of substituents, viz, ortho, meta, para, also affect the electronic properties of the substituents. Without being bound to any particular type or level of theory, it is known that ortho- and para-disposed substituents electronically affect one another to a greater degree than do corresponding meta-disposed substituents. Meta-disubstituted aromatics are often synthesized using different routes than are corresponding ortho and para-disubstituted aromatics.

The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

The term "perhaloalkyl" refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

The substituent R or R' appearing by itself and without a number designation refers to an optionally substituted substituent selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon).

A "sulfinyl" group refers to a -S(=O)-R group, with R as defined herein.

A "N-sulfonamido" group refers to a $RS(=O)_2NH$- group with R as defined herein.

A "S-sulfonamido" group refers to a $-S(=O)_2NR_2$, group, with R as defined herein.

An "N-thiocarbamyl" group refers to an $ROC(=S)NH$- group, with R as defined herein.

An "O-thiocarbamyl" group refers to a $-OC(=S)-NR$, group with R as defined herein.

A "thiocyanato" group refers to a -CNS group.

A "trihalomethanesulfonamido" group refers to a $X_3CS(=O)_2NR$- group with X and R as defined herein.

A "trihalomethanesulfonyl" group refers to a $X_3CS(=O)_2$- group where X is a halogen.

Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from alkyl, perhaloalkyl, perhaloalkoxy, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

Molecular embodiments of the present invention may possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

In some situations, compounds may exist as tautomers. All tautomers are included within Formula I and are provided by this invention.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

METHODS OF MODULATING PROTEIN FUNCTION

In another aspect, the present invention relates to a method of modulating at least one peroxisome proliferator-activated receptor (PPAR) function comprising the step of contacting the PPAR with a compound of Formula I, as described herein. The change in cell phenotype, cell proliferation, activity of the PPAR, or binding of the PPAR with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like. In certain embodiments, the PPAR may be selected from the group consisting of PPARα, PPARδ, and PPARγ.

The term "activate" refers to increasing the cellular function of a PPAR. The term "inhibit" refers to decreasing the cellular function of a PPAR. The PPAR function may be the interaction with a natural binding partner or catalytic activity.

The term "cell phenotype" refers to the outward appearance of a cell or tissue or the function of the cell or tissue. Examples of cell or tissue phenotype are cell size (reduction or enlargement), cell proliferation (increased or decreased numbers of cells), cell differentiation (a change or absence of a change in cell shape), cell survival, apoptosis (cell death), or the utilization of a metabolic nutrient (e.g., glucose uptake). Changes or the absence of changes in cell phenotype are readily measured by techniques known in the art.

The term "cell proliferation" refers to the rate at which a group of cells divides. The number of cells growing in a vessel can be quantified by a person skilled in the art when that person visually counts the number of cells in a defined area using a common light microscope. Alternatively, cell proliferation rates can be quantified by laboratory apparatus that optically measure the density of cells in an appropriate medium.

The term “contacting” as used herein refers to bringing a compound of this invention and a target PPAR together in such a manner that the compound can affect the activity of the PPAR, either directly; i.e., by interacting with the PPAR itself, or indirectly; i.e., by interacting with another molecule on which the activity of the PPAR is dependent. Such “contacting” can be accomplished in a test tube, a petri dish, a test organism (e.g., murine, hamster or primate), or the like. In a test tube, contacting may involve only a compound and a PPAR of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that environment. In this context, the ability of a particular compound to affect a PPAR related disorder; i.e., the IC_{50} of the compound can be determined before use of the compounds in vivo with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well-known to those skilled in the art, to get the PPARs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

The term “modulate” refers to the ability of a compound of the invention to alter the function of a PPAR. A modulator may activate the activity of a PPAR, may activate or inhibit the activity of a PPAR depending on the concentration of the compound exposed to the PPAR, or may inhibit the activity of a PPAR. The term “modulate” also refers to altering the function of a PPAR by increasing or decreasing the probability that a complex forms between a PPAR and a natural binding partner. A modulator may increase the probability that such a complex forms between the PPAR and the natural binding partner, may increase or decrease the probability that a complex forms between the PPAR and the natural binding partner depending on the concentration of the compound exposed to the PPAR, and or may decrease the probability that a complex forms between the PPAR and the natural binding partner.

The term “monitoring” refers to observing the effect of adding the compound of the invention to the cells of the method. The effect can be manifested in a change in cell phenotype, cell proliferation, PPAR activity, or in the interaction between a PPAR and a natural binding partner. Of course, the term “monitoring” includes detecting whether a change has in fact occurred or not.

Exemplary Assays

The following assay methods are provided by way of example only. Compounds may be tested for their ability to bind to hPPAR-gamma, hPPAR-alpha, or PPAR-delta using a Scintillation Proximity Assay (SPA). The PPAR ligand binding domain (LBO) may be expressed in E. coli as polyHis tagged fusion proteins and purified. The LBO is then labeled with biotin and immobilized on streptavidin modified scintillation proximity beads. The beads are then incubated with a constant amount of the appropriate radioligand eH-BRL 49653 for PPARγ, 2-(4(2-(2,3-Ditritio-1-heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenoxy)-2 methyl butanoic acid (described in WO1008002) for hPPAR-alpha and GW 2433 (see Brown, P. J et al . *Chem. Biol.* **1997**, *4*, 909-918. For the structure and synthesis of this ligand) for PPAR-delta) and variable concentrations of test compound, and after equilibration the radioactivity bound to the beads is measured by a scintillation counter. The amount of nonspecific binding, as assessed by control wells containing 50 μM of the corresponding unlabelled ligand, is subtracted from each data point. For each compound tested, plots of ligand concentration vs. CPM of radioligand bound are constructed and apparent K, values are estimated from nonlinear least squares fit of the data assuming simple competitive binding. The details of this assay have been reported elsewhere (see, Blanchard, S. G. et. al., "Development of a Scintillation Proximity Assay for Peroxisome Proliferator-Activated Receptor gamma Ligand Binding Domain" Anal. Biochem. 1998, 257, 112-119).

Tranfection Assays

The following transfection assay methods are provided by way of example only. Compounds may be screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR subtypes (transactivation assay). A previously established chimeric receptor system was utilized to allow comparison of the relative transcriptional activity of the receptor subtypes on the same target gene and to prevent endogenous receptor activation from complicating the interpretation of results. See, for example, Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A; Wilkinson, W.O.; Willson, T. M.; Kliewer, S. A., An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ), *J. Biol. Chem.*, 1995, 270, 12953-6. The ligand binding domains for murine and human PPAR-alpha, PPAR-gamma, and PPAR-delta are each fused to

the yeast transcription factor GAL4 DNA binding domain. CV-1 cells were transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct containing five copies of the GAL4 DNA binding site driving expression of secreted placental alkaline phosphatase (SPAP) and p-galactosidase. After 16 h, the medium is exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24 h, cell extracts are prepared and assayed for alkaline phosphatase and pgalactosidase activity. Alkaline phosphatase activity was corrected for transfection efficiency using the p-galactosidase activity as an internal standard (see, for example, Kliewer, S. A., et. al. Cell 1995, 83, 813-819. Rosiglitazone is used as a positive control in the hPPARγ assay. The positive control in the hPPAR-alpha and hPPAR-delta assays was 2-[4-(2-(3-(4-fluorophenyl)-1heptylureido)ethyl)-phenoxy]-2-methylpropionic acid, which can be prepared as described in Brown, Peter J., et. al. Synthesis (7), 778-782 (1997), or patent publication WO 9736579.

TARGET DISEASES TO BE TREATED

In another aspect, the present invention relates to a method of treating a disease comprising identifying a patient in need thereof, and administering a therapeutically effective amount of a compound of Formula I, as described herein, to the patient.

Biological processes modulated by PPAR are those modulated by receptors, or receptor combinations, which are responsive to the PPAR receptor ligands described herein. These processes include. for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinemia (resulting from, for example, abnormal pancreatic beta cell function, insulin secreting tumors and/or autoimmune hypoglycemia due to autoantibodies to insulin, the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which lead to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, and adipocyte differentiation.

Non-insulin-dependent diabetes mellitus (NIDDM), or Type 2 diabetes, is the more common form of diabetes, with 90-95% of hyperglycemic patients experiencing

this form of the disease. Resistance to the metabolic actions of insulin is one of the key features of non-insulin dependent diabetes (NIDDM). Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin-sensitive target organs, for example, adipocytes and skeletal muscle, and by impaired inhibition of hepatic glucose output. The functional insulin deficiency and the failure of insulin to suppress hepatic glucose output results in fasting hyperglycemia. Pancreatic β-cells compensate for the insulin resistance by secreting increased levels of insulin. However, the β-cells are unable to maintain this high output of insulin, and, eventually, the glucose-induced insulin secretion falls, leading to the deterioration of glucose homeostasis and to the subsequent development of overt diabetes.

Compelling evidence has shown that PPARγ is a valuable molecular target for development of drugs for treatment of insulin resistance (see Willson, et al. J. Med. Chem. 43: 527-550 (2000)). In fact, PPARγ agonists rosiglitazone (Avandia) and pioglitazone (Actos) are insulin sensitizers and are currently marketed drugs for treatment of type 2 diabetes.

Obesity is an excessive accumulation of adipose tissue. Recent work in this area indicates that PPARγ plays a central role in the adipocyte gene expression and differentiation. Excess adipose tissue is associated with the development of serious medical conditions, for example, non-insulin-dependent diabetes mellitus (NIDDM), hypertension, coronary artery disease, hyperlipidemia obesity and certain malignancies. The adipocyte may also influence glucose homeostasis through the production of tumor necrosis factor α (TNFα) and other molecules. PPARγ activators, in particular Troglitazone®, have been found to convert cancerous tissue to normal cells in liposarcoma, a tumor of fat (PNAS 96:3951-3956, 1999). Therefore, PPARγ activators may be useful in the treatment of obesity and breast and colon cancer.

Moreover, PPARγ activators, for example Troglitazone®, have been implicated in the treatment of polycystic ovary syndrome (PCO). This is a syndrome in women that is characterized by chronic anovulation and hyperandrogenism. Women with this syndrome often have insulin resistance and an increased risk for the development of non insulin-dependent diabetes mellitus. (Dunaif, Scott, Finegood, Quintana, Whitcomb, J. Clin. Endocrinol. Metab., 81:3299,1996.

Furthermore, PPARγ activators have recently been discovered to increase the production of progesterone and inhibit steroidogenesis in granulosa cell cultures and

therefore may be useful in the treatment of climacteric. (USP 5,814,647 Urban et al. September 29,1998; B. Lohrke et al. Journal of Edocrinology, 159,429-39, 1998). Climacteric is defined as the syndrome of endocrine, somatic and psychological changes occurring at the termination of the reproductive period in the female.

PPARα is activated by a number of medium and long-chain fatty acids and is involved in stimulating β-oxidation of fatty acids in tissues such as liver, heart, skeletal muscle, and brown adipose tissue (Isseman and Green, supra; Beck et al., Proc. R. Soc. Lond. 247:83-87,1992; Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657, 1992). Pharmacological PPARα activators, for example fenofibrate, clofibrate, genfibrozil, and bezafibrate. are also involved in substantial reduction in plasma triglycerides along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia, hyperlipidemia and obesity. PPARα is also known to be involved in inflammatory disorders. (Schoonjans, K., Current Opinion in Lipidology, 8, 159-66, 1997).

PPARα agonists may also be useful in raising HDL levels and therefore may be useful in treating atherosclerotic diseases. (Leibowitz et al.; WO/9728149). . Atherosclerotic diseases include vascular disease, coronary heart disease, cerebrovascular disease and peripheral vessel disease. Coronary heart disease includes CHD death, myocardial infarction, and coronary revascularization. Cerebrovascular disease includes ischemic or hemorrhagic stroke and transient ischemic attacks.

The third subtype of PPARs, PPARδ (PPARβ, NUC1), is broadly expressed in the body and has been shown to be a valuable molecular target for treatment of dyslipedimia and other diseases. For example, in a recent study in insulin-resistant obese rhesus monkeys, a potent and selective PPARδ compound was shown to decrease VLDL and increase HDL in a dose response manner (Oliver et al., Proc. Natl. Acad. Sci. U. S. A.98: 5305, 2001).

Compounds described herein may be activating both PPARα and PPARγ, or PPARδ and PPARγ, or all three PPAR subtypes and therefore may be used in the treatment of dyslipidemia associated with atherosclerosis, non-insulin dependent diabetes mellitus, metabolic syndrome X, (Staels, B. et al., Curr. Pharm. Des., 3 (1),1-14 (1997)) and familial combined hyperlipidemia (FCH). Metabolic syndrome X is the syndrome characterized by an initial insulin resistant state, generating hyperinsulinaemia, dyslipidaemia and impaired glucose tolerance, which can progress

to non-insulin dependent diabetes mellitus (Type 2 diabetes), characterized by hyperglycemia. FCH is characterized by hypercholesterolemia and hypertriglyceridemia within the same patient and family.

Thus, in certain embodiments, the disease to be treated by the methods of the present invention is selected from the group consisting of obesity, diabetes, hyperinsulinemia, metabolic syndrome X, polycystic ovary syndrome, climacteric, disorders associated with oxidative stress, inflammatory response to tissue injury, pathogenesis of emphysema, ischemia-associated organ injury, doxorubicin-induced cardiac injury, drug-induced hepatotoxicity, atherosclerosis, and hypertoxic lung injury.

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention relates to a pharmaceutical composition comprising a compound of Formula I, as described herein, and a pharmaceutically acceptable diluent, excipient, or carrier.

The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as carriers, diluents or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The term "carrier" refers to relatively nontoxic chemical compounds or agents. Such carriers may facilitate the incorporation of a compound into cells or tissues. For example, human serum albumin (HSA) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (providing pH control) are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline. It is a buffer found naturally in the blood system. Since buffer salts can control the pH of a solution at

low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

The term "physiologically acceptable" refers to a carrier or diluent that does not abrogate the biological activity or properties of the compound, and is nontoxic.

The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutically acceptable salts may be obtained by reacting a compound of the invention with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutically acceptable salts may also be obtained by reacting a compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods known in the art

A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

The compounds described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant

application may be found in "Remington's Pharmaceutical Sciences," 20th ed. Edited by Alfonso Gennaro, 2000.

Routes Of Administration

Suitable routes of administration may, for example, include oral, rectal, transmucosal, pulmonary, ophthalmic or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

Composition/Formulation

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

For intravenous injections, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, the agents of the invention may be formulated in aqueous or nonaqueous

solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers or excipients well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more compound of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be

administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a 10% ethanol, 10% polyethylene glycol 300, 10% polyethylene glycol 40 castor oil (PEG-40 castor oil) with 70% aqueous solution. This cosolvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a cosolvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the cosolvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of PEG-40 castor oil, the fraction size of polyethylene glycol 300 may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides maybe included in the aqueous solution.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as N-methylpyrrolidone also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

TREATMENT METHODS, DOSAGES AND COMBINATION THERAPIES

The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits.

The term "therapeutically effective amount" as used herein refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disease, condition or disorder being treated. In reference to the treatment of diabetes or dyslipidemia a therapeutically effective amount refers to that amount which has the effect of (1) reducing the blood glucose levels; (2) normalizing lipids, e.g. triglycerides, low-density lipoprotein; and/or (3) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the disease, condition or disorder to be treated.

The compositions containing the compound(s) described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease, condition or disorder mediated, modulated or involving the PPARs, including but not limited to metabolic diseases, conditions, or disorders, as described above, in an amount sufficient to cure or at least partially arrest the symptoms of the disease, disorder or condition. Amounts effective for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. It is considered well within the skill of the art for one to determine such therapeutically effective amounts by routine experimentation (e.g., a dose escalation clinical trial).

In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition mediated, modulated or involving the PPARs, including but not limited to metabolic diseases, conditions, or disorders, as described above. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. It is considered well within the skill of the art for one to determine such prophylactically effective amounts by routine experimentation (e.g., a dose escalation clinical trial).

The terms "enhance" or "enhancing" means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of

therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system. When used in a patient, amounts effective for this use will depend on the severity and course of the disease, disorder or condition (including, but not limited to, metabolic disorders), previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. It is considered well within the skill of the art for one to determine such enhancing-effective amounts by routine experimentation.

Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. When the symptoms have been alleviated to the desired level, treatment can cease. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, preferably 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, amide, prodrug, or solvate) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant

may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

Specific, non-limiting examples of possible combination therapies include use of the compound of formula (I) with: (a) stating and/or other lipid lowering drugs for example MTP inhibitors and LDLR upregulators; (b) antidiabetic agents, e.g. metformin, sulfonylureas, or PPAR-gamma, PPAR-alpha and PPAR-alpha/gamma modulators (for example thiazolidinediones such as e.g. Pioglitazone and Rosiglitazone); and (c) antihypertensive agents such as angiotensin antagonists, e.g., telmisartan, calcium channel antagonists, e.g. lacidipine and ACE inhibitors, e.g., enalapril.

In any case, the multiple therapeutic agents (one of which is one of the compounds described herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may vary from more than zero weeks to less than four weeks.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

Compounds of the present invention may be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. As a guide the following synthetic methods may be utilized.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

Selected examples of covalent linkages and precursor functional groups which yield them are given in the Table entitled "Examples of Covalent Linkages and Precursors Thereof." Precursor functional groups are shown as electrophilic groups and nucleophilic groups. The functional group on the organic substance may be attached directly, or attached via any useful spacer or linker as defined below.

Table 1: Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines
Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols
Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols

Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols

In general, carbon electrophiles are susceptible to attack by complementary nucleophiles, including carbon nucleophiles, wherein an attacking nucleophile brings an electron pair to the carbon electrophile in order to form a new bond between the nucleophile and the carbon electrophile.

Suitable carbon nucleophiles include, but are not limited to alkyl, alkenyl, aryl and alkynyl Grignard, organolithium, organozinc, alkyl-, alkenyl , aryl- and alkynyl-tin reagents (organostannanes), alkyl-, alkenyl-, aryl- and alkynyl-borane reagents (organoboranes and organoboronates); these carbon nucleophiles have the advantage of being kinetically stable in water or polar organic solvents. Other carbon nucleophiles include phosphorus ylids, enol and enolate reagents; these carbon nucleophiles have the advantage of being relatively easy to generate from precursors well known to those skilled in the art of synthetic organic chemistry. Carbon nucleophiles, when used in conjunction with carbon electrophiles, engender new carbon-carbon bonds between the carbon nucleophile and carbon electrophile.

Non-carbon nucleophiles suitable for coupling to carbon electrophiles include but are not limited to primary and secondary amines, thiols, thiolates, and thioethers, alcohols, alkoxides, azides, semicarbazides, and the like. These non-carbon nucleophiles, when used in conjunction with carbon electrophiles, typically generate heteroatom linkages (C-X-C), wherein X is a hetereoatom, e. g, oxygen or nitrogen.

Use of Protecting Groups

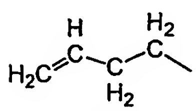
The term "protecting group" refers to chemical moieties that block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal.

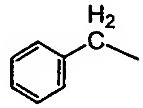
Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

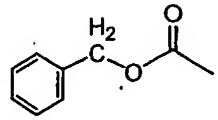
Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

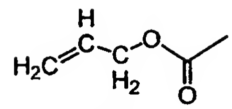
Allyl blocking groups are useful in then presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd_0-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

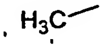
Typically blocking/protecting groups may be selected from:

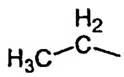

allyl

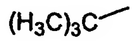

Bn

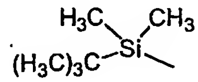

Cbz

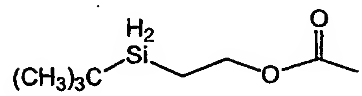

alloc

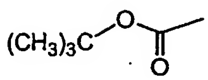

Me

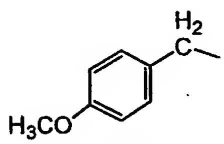

Et

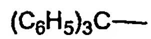

t-butyl

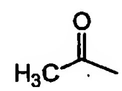

TBDMS

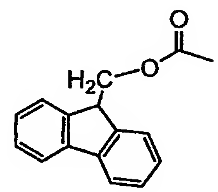

Teoc


Boc


pMBn


trityl


acetyl


Fmoc

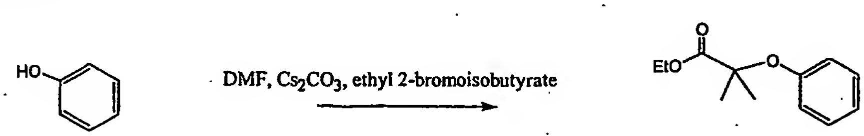
Other protecting groups are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

GENERAL SYNTHETIC METHODS FOR PREPARING COMPOUNDS

Molecular embodiments of the present invention can be synthesized using standard synthetic techniques known to those of skill in the art. Compounds of the present invention can be synthesized using the general synthetic procedures set forth in Scheme I. Specific synthetic procedures are set forth in subsequent schemes.

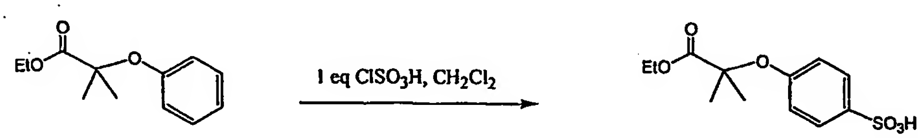
SCHEME I

A)

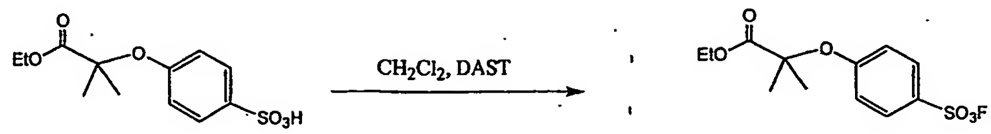


Ia Ib

B)

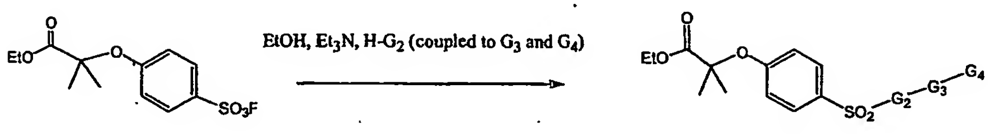


Ib Ic

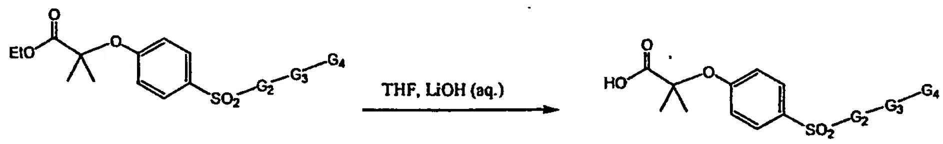


C) Ic Id

D)



Id Ie

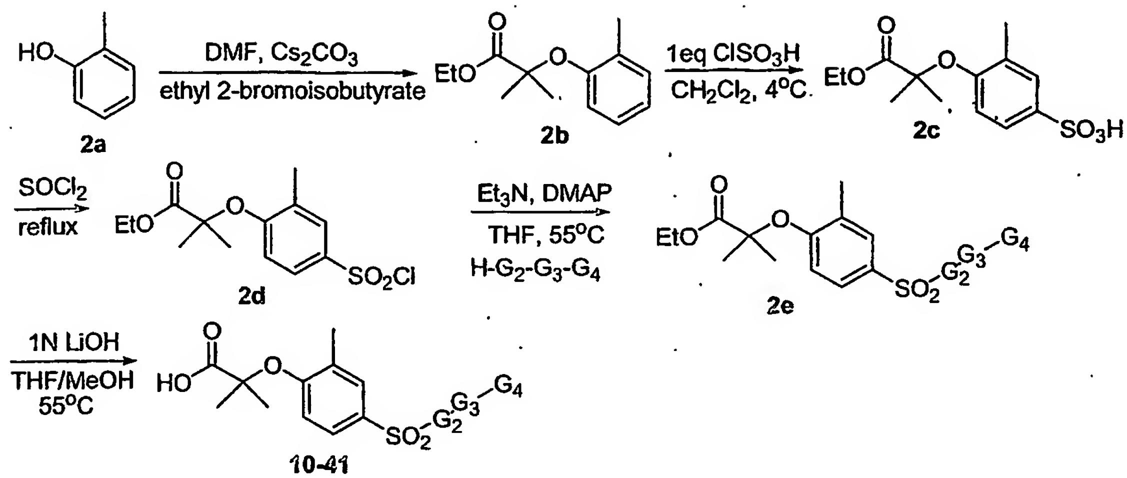


Ie

E) If

Scheme I sets forth five steps, A-E. In a first step, the hydroxy functional group of phenol or phenol derivative **Ia** is functionalized to yield acid-protected intermediate **Ib**. Suitable protecting groups include but are not limited to esters and other readily hydrozyable protecting groups. In a second step (B), intermediate **Ib** is sulfonated to yielded sulfonated intermediate **Ic**. In a third step (C), the sulfonyl moiety is halogenated to give electrophilic species **Id**, which comprises a suitable leaving group. Suitable leaving groups include but are not limited to halides, F, Cl. In a subsequent step, the leaving group F of intermediate **Id** is displaced with an incoming group H-G_2, for example, a group comprising a nitrogen nucleophile to yield a protected product, intermediate **Ie**. Group G_2 may or may not be connected to additional groups G_3 and G_4 as defined herein. In a subsequent step, the ester protecting group is hydrolytically cleaved to yield products as embodied by examples 1-41 disclosed herein.

SCHEME II



Scheme II presents a general procedure for synthesizing compounds 10-41 described herein.

PREPARATION OF INTERMEDIATES Ib-e (See Scheme I):

INTERMEDIATE Ib: 2-Methyl-2-phenoxy-propionic acid ethyl ester.

Phenol (2.0 g, 21.3 mmol), ethyl 2-bromoisobutyrate (3.28 mL, 22.3 mmol) and cesium carbonate (10.39 g, 31.9 mmol) were mixed in DMF (10 mL) overnight at 60 °C with vigorous stirring. The resulting mixture was then diluted with water (50 mL) and extracted with dichloromethane (50 mL). The organic fraction was then extracted with 1.0 N NaOH (50 mL) before being dried over Na_2SO_4 and evaporated to leave the desired compound as a clear oil (2.48 g, 11.9 mmol, 56 %) pure enough for the next step.

^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 7.23 (t, 2H), 6.98 (t, 1H), 6.84 (d, 2H), 4.23 (q, 2H), 1.59 (s, 6H), 1.24 (t, 3H) ppm. LCMS (ES+): 231 $[MNa]^+$ m/e.

INTERMEDIATE 1c: 2-Methyl-2-(4-sulfo-phenoxy)-propionic acid ethyl ester

Ethyl ester (**1b**, 546 mg, 2.62 mmol) was dissolved in 10 mL CH_2Cl_2 and the resulting solution was cooled to ice temperature before chlorosulfonic acid (175 μL, 2.62 mmol) was carefully added via syringe. The resulting clear solution was then allowed to return to room temperature with stirring. After 30 minutes, the volatiles were removed under high-vacuum to leave the desired compound as a highly deliquescent pink crystalline solid (quantitative) which was quickly used in the next reaction. It had LCMS (ES-): 287 $[M:]^-$ m/e.

INTERMEDIATE 1d: 2-(4-Fluorosulfonyl-phenoxy)-2-methyl-propionic acid ethyl ester

Sulfonic acid intermediate **1c** (8.94 g, 31.0 mmol) was dissolved in 50 ml CH_2Cl_2 in a Teflon container before DAST (5.0 g, 31.0 mmol) was added via syringe. After stirring at room temperature, TLC shows the reaction to be complete after 2 hours. The volatiles were removed and the resulting oil was subjected to column chromatography leaving the desired compound as a clear viscous oil (8.13 g, 28.0 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 7.89 (d, 2H), 6.94 (d, 2H), 4.23 (q, 2H), 1.69 (s, 6H), 1.23 (t, 3H) ppm.

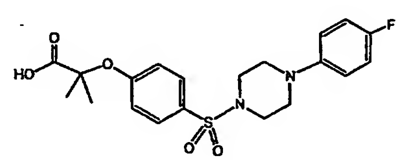
Syntheses for Examples 1-9

Intermediate **1d** is suitable for coupling to wide variety of nucleophilic amines using the following general procedures, substituting the amino components as required. The following synthetic example may be used to prepare the compounds of Examples 1-9.

INTERMEDIATE 1e: 2-{4-[4-(4-Fluoro-phenyl)-piperazine-1-sulfonyl]-phenoxy}-2-methyl-propionic acid ethyl ester.

Sulfonyl fluoride intermediate **1d**, (91 mg, 0.31 mmol) was dissolved in 1 ml ethanol followed by 1-(4-fluoro-phenyl)-piperazine (68 mg, 0.38 mmol). Triethyl amine (210 μl) was added last and the resulting solution was heated to 60 °C (sealed vessel) overnight with stirring. Removal of the volatiles leaves a dark solid which was purified by radial chromatography to leave the desired compound **1e**, as a clear viscous oil (92 mg, 0.20 mmol, 65 %). LCMS (ES+): 451 $[MH]^+$ m/e.

Example 1



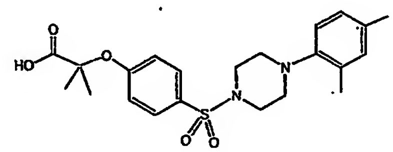
2-{4-[4-(4-Fluoro-phenyl)-piperazine-1-sulfonyl]-phenoxy}-2-methyl-propionic acid

Sulfonamide **1e** (93 mg, 0.20 mmol) was dissolved in 1 ml THF before 1.0 N LiOH (500 μl) was added. The resulting mixture was then vigorous stirred overnight at room temperature. The mixture was then neutralized by addition of 1.0 N HCl (500 μl). Ethyl acetate (5 ml) was then added and the organic fraction was dried over Na_2SO_4 before being evaporated to leave a clear oil. The oil was then recrystallized from ethyl acetate/hexanes to yield the desired compound as a clear crystalline solid

(77 mg, 0.18 mmol, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.70 (d, 2H), 6.98 (m, 4H), 6.84 (m, 2H), 3.16 (s, 8H), 1.70 (s, 6H) ppm.

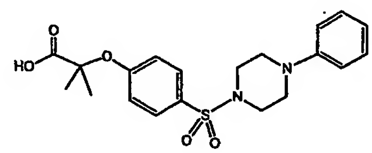
^{1}H NMR DATA FOR EXAMPLES 2-9

Example 2



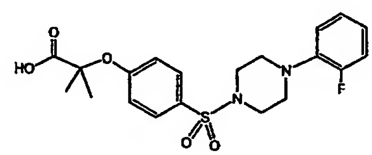
2-{4-[4-(2,4-Dimethyl-phenyl)-piperazine-1-sulfonyl]-phenoxy}-2-methyl-propionic acid ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.71 (d, 2H), 7.02 (dd, 2H), 7.00 (m, 2H), 6.98 (d, 1H), 3.15 (bs, 4H), 2.94 (t, 4H), 2.26 (s, 3H), 2.16 (s, 3H), 1.71 (s, 6H) ppm.

Example 3



2-Methyl-2-[4-(4-phenyl-piperazine-1-sulfonyl)-phenoxy]-propionic acid ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 13.25 (bs, 1H), 7.68 (d, 2H), 7.20 (dd, 2H), 7.01 (d, 2H), 6.90 (dd, 2H), 6.80 (m, 1H), 3.19 (t, 4H), 2.97 (t, 4H), 1.58 (s, 6H) ppm.

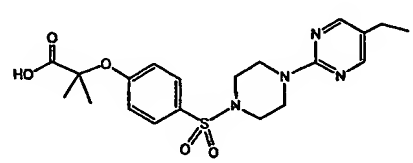
Example 4



2-{4-[4-(2-Fluoro-phenyl)-piperazine-1-sulfonyl]-phenoxy}-2-methyl-propionic acid

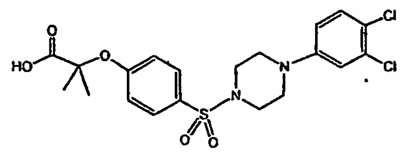
^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 13.30 (bs, 1H), 7.69 (d, 2H), 7.10 (m, 2H), 7.01 (d, 2H), 6.99 (m, 2H), 3.07 (t, 4H), 3.00 (t, 4H), 1.59 (s, 6H) ppm.

Example 5



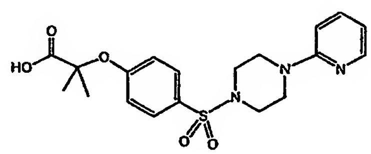
2-{4-[4-(5-Ethyl-pyrimidin-2-yl)-piperazine-1-sulfonyl]-phenoxy}-2-methyl-propionic acid ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 8.22 (s, 2H), 7.52 (d, 2H), 6.91 (d, 2H), 3.77 (t, 4H), 2.87 (t, 4H), 2.40 (q, 2H), 1.40 (s, 6H), 1.10 (t, 3H) ppm.

Example 6



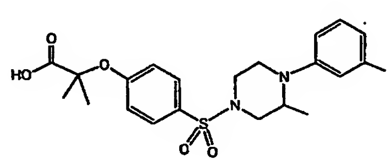
2-{4-[4-(3,4-Dichloro-phenyl)-piperazine-1-sulfonyl]-phenoxy}-2-methyl-propionic acid ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 13.25 (bs, 1H), 7.68 (d, 2H), 7.40 (d, 1H), 7.12 (d, 1H), 7.00 (d, 2H), 6.90 (dd, 1H), 3.25 (t, 4H), 2.95 (t, 4H), 1.58 (s, 6H) ppm.

Example 7



2-Methyl-2-[4-(4-pyridin-2-yl-piperazine-1-sulfonyl)-phenoxy]-propionic acid ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 13.25 (bs, 1H), 8.08 (d, 1H), 7.66 (d, 2H), 7.52 (dd, 1H), 6.98 (d, 2H), 6.80 (d, 1H), 6.65 (dd, 1H), 3.57 (t, 4H), 2.93 (t, 4H), 1.57 (s, 6H) ppm.

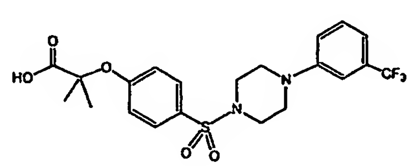
Example 8



2-Methyl-2-[4-(3-methyl-4-m-tolyl-piperazine-1-sulfonyl)-phenoxy]-propionic acid

^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 13.40 (bs, 1H), 7.67 (d, 2H), 7.08 (dd, 1H), 7.00 (d, 2H), 6.67 (m, 2H), 6.60 (d, 1H), 3.99 (m, 1H), 3.47 (d, 1H), 3.26 (m, 2H), 3.02 (m, 1H), 2.58 (m, 1H), 2.42 (m, 1H), 2.20 (s, 3H), 1.59 (s, 6H), 0.95 (d, 3H) ppm.

Example 9



2-Methyl-2-{4-[4-(3-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-phenoxy}-propionic acid ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 13.25 (bs, 1H), 7.69 (d, 2H), 7.41 (dd, 1H), 7.19 (d, 1H), 7.17 (s, 1H), 7.09 (d, 1H), 7.00 (d, 2H), 3.30 (t, 4H), 2.98 (t, 4H), 1.58 (s, 6H) ppm.

<u>Syntheses for Examples 10-41</u>

Examples 10-41 were prepared under modified conditions from intermediate **2d** (See Scheme II).

Synthesis of Intermediate 2b 2-Methyl-2-*o*-toloxy-propionic acid ethyl ester. Intermediate **2b** was prepared from *o*-cresol followed the procedure for intermediate **1b**.. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.14 (d, 1H), 7.04 (t, 1H), 6.88 (t, 1H), 6.66 (d, 1H), 4.24 (q, 2H), 2.24 (s, 3H), 1.57 (s, 6H), 1.25 (t, 3H).

2-(4-Chlorosulfonyl-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (2d). A solution of intermediate **2b** (1.19g, 5.35 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was cooled to 0°C. To this cold solution was added $ClSO_3H$ (356 mL, 5.35 mmol, 1.0 equiv) dropwise with stirring. After stirred at same temperature for 10 min, the reaction mixture was concentrated on rotavapor under reduced pressure to give intermediate **2c**, which was used directly in the following step.

To the above crude intermediate **2c** was added thionyl chloride at room temperature with stirring. The resulting mixture was heated to reflux and kept refluxing for 20 min. After removal of the excessive thionyl chloride under reduced pressure on rotavapor, the residue was purified by chromatography to give 1.23 g (66% for two steps) of desired intermediate **2d**.. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.82 (s, 1H), 7.74 (d, 1H), 6.67 (d, 1H), 4.23 (q, 2H), 2.30 (s, 3H), 1.68 (s, 6H), 1.22 (t, 3H).

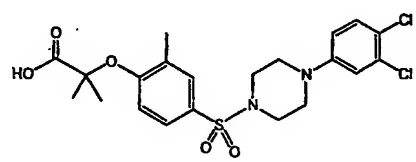
Parallel synthesis of piperazine sulfonamides (10-41). Phenyl chlorosulfonyl- **2d** (15.14 g, 47.17 mmol) was dissolved in THF (75 mL) and this resulting solution was allotted to 32 vials charged with different 4-aryl piperazines (1.47 mmol, 1.0 equiv) (each with 2.5 mL of solution). To each of the above 32 reaction mixtures was added NEt_3 (411 µL, 2.95 mmol, 2.0 equiv) followed by catalytic amount of DMAP and 5 mL of THF. The resulting suspensions were heated to 55°C and stirred at same temperature for 18 hours. The reaction mixtures were concentrated under N_2 blow. The residues were diluted with ethyl acetate (15 mL) and

then washed with water, saturated $NaHCO_3$, brine and dried over Na_2SO_4. After removal of solvent, the crude products were purified by chromatography to give 32 desired intermediates with 20-75% yield.

The 32 Intermediates were charged in 32 vials, respectively. To each of the vials was added THF/MeOH (3:1) (5 mL) and then corresponding amount of 1N LiOH (2.0 equiv) to each of the resulting solutions. The resulting mixtures were stirred at room temperature for 6 hours and then concentrated under N_2 blow. The residues were partitioned with diethyl ether (5 mL) and H_2O (5 mL). After separation, the aqueous solutions were neutralized with corresponding amounts of 1N HCl (2.0 equiv) and extracted with ethyl acetate (10 mL). The organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent, products **10-41** were obtained with 50-85% yields.

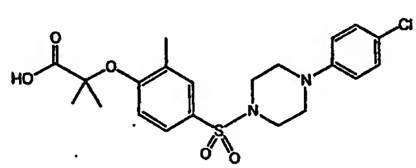
^{1}H NMR DATA FOR EXAMPLES 10-41

Example 10



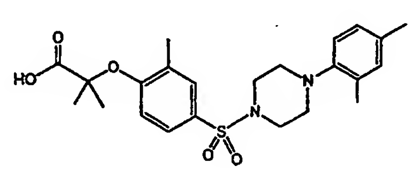
2-{4-[4-(3, 4-dichlorophenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.56 (s, 1H), 7.50 (d, 1H), 7.26 (d, 1H), 6.91 (s, 1H), 6.78 (d, 1H), 6.67 (d, 1H), 3.21 (t, 4H), 3.12 (t, 4H), 2.28 (s, 3H), 1.69 (s, 6H).

Example 11



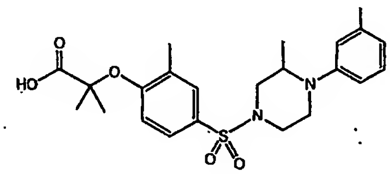
2-{4-[4-(4-Chloro-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.57 (s, 1H), 7.54 (d, 1H), 7.18 (d, 2H), 6.78 (d, 3H), 3.20 (t, 4H), 3.15 (t, 4H), 2.28 (s, 3H), 1.70 (s, 6H).

Example 12



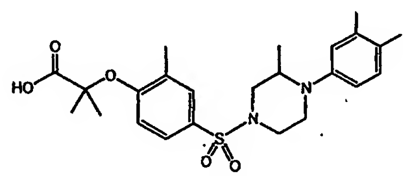
2-{4-[4-(2,4-Dimethyl-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.58 (s, 1H), 7.53 (d, 1H), 6.96 (d, 2H), 6.89 (d, 1H), 6.82 (d, 1H), 3.15 (m, 4H), 2.94 (t, 4H), 2.31 (s, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 1.70 (s, 6H).

Example 13



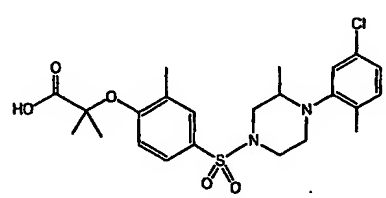
2-Methyl-2-[2-methyl-4-(3-methyl-4-*m*-tolyl-piperazine-1-sulfonyl)-phenoxy]-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.55 (s, 1H), 7.70 (d, 1H), 7.13 (t, 1H), 6.77 (m, 4H), 3.78 (m, 1H), 3.42 (m, 1H), 3.20 (m, 3H), 3.00 (m, 1H), 2.84 (m, 1H), 2.28 (d, 6H), 1.66 (s, 6H), 1.05 (d, 3H).

Example 14



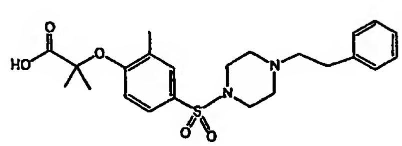
2-{4-[4-(3,4-Dimethyl-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.57 (s, 1H), 7.50 (d, 1H), 7.00 (d, 2H), 6.77 (d, 1H), 6.72 (s, 1H), 6.68 (d, 1H), 3.16 (m, 8H), 2.28 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 1.67 (s, 3H).

Example 15



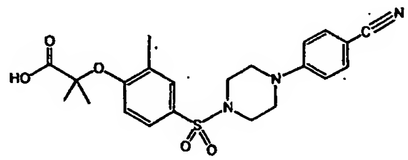
2-{4-[4-(5-Chloro-2-methyl-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.58 (s, 1H), 7.53 (d, 1H), 7.06 (d, 2H), 6.97 (s, 1H), 6.93 (d, 1H), 6.81 (d, 1H), 3.15 (m, 4H), 2.94 (t, 4H), 2.30 (s, 3H), 2.14 (s, 3H), 1.71 (s, 3H).

Example 16



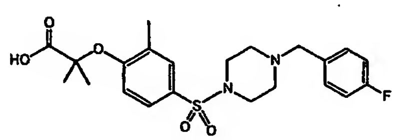
2-Methyl-2-[2-methyl-4-(4-phenethyl-piperazine-1-sulfonyl)-phenoxy]-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.50 (s, 1H), 7.40 (d, 1H), 7.26 (m, 3H), 7.21 (d, 2H), 6.80 (d, 2H), 3.28 (m, 4H), 3.18 (t, 4H), 3.10 (t, 4H), 2.26 (s, 3H), 1.66 (s, 6H).

Example 17



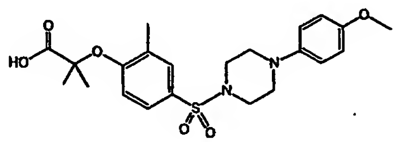
2-{4-[4-(4-Cyano-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.55 (s, 1H), 7.51 (d, 1H), 7.48 (d, 2H), 6.83 (d, 2H), 6.77 (d, 1H), 3.39 (t, 4H), 3.12 (t, 4H), 2.27 (s, 3H), 1.69 (s, 6H).

Example 18



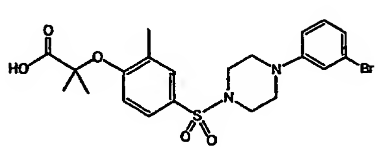
2-{4-[4-(4-Fluoro-benzyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.48 (s, 1H), 7.40 (m, 3H), 7.04 (d, 1H), 7.01 (d, 1H), 6.68 (d, 1H), 3.98 (s, 2H), 3.24 (s, 4H), 3.04 (s, 4H), 2.22 (s, 3H), 1.55 (s, 6H).

Example 19



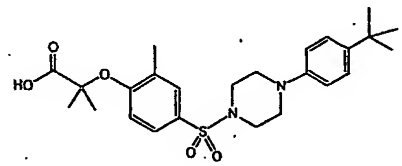
2-{4-[4-(4-Methoxy-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.55 (s, 1H), 7.50 (d, 1H), 6.90 (d, 2H), 6.83 (d, 2H), 6.75 (d, 1H), 3.75 (s, 3H), 3.15 (s, 8H), 2.27 (s, 3H), 1.65 (s, 6H).

Example 20



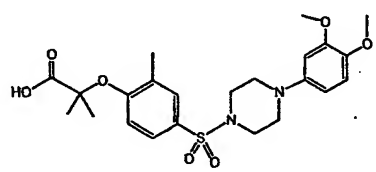
2-{4-[4-(3-Bromo-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.56 (s, 1H), 7.52 (d, 1H), 7.26 (t, 1H), 6.99 (d, 2H), 6.76 (d, 2H), 3.22 (t, 4H), 3.13 (t, 4H), 2.28 (s, 3H), 1.69 (s, 6H).

Example 21



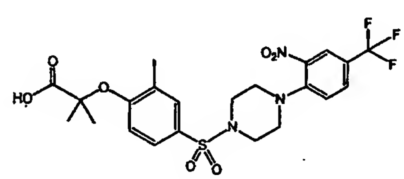
2-{4-[4-(4-t-butyl -phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.56 (s, 1H), 7.52 (d, 1H), 7.28 (d, 2H), 6.87 (d, 2H), 6.77 (d, 1H), 3.20 (t, 4H), 3.16 (t, 4H), 2.28 (s, 3H), 1.67 (s, 6H), 1.25 (s, 9H).

Example 22



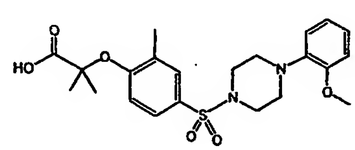
2-{4-[4-(3,4-Dimethoxy-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.55 (s, 1H), 7.49 (d, 1H), 6.74 (d, 1H), 6.55 (s, 1H), 6.46 (d, 1H), 3.81 (s, 6H), 3.15 (s, 8H), 2.26 (s, 3H), 1.65 (s, 6H).

Example 23



2-{4-[4-(2-Nitro, 4-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 8.03 (s, 1H), 7.70 (d, 1H), 7.53 (s, 1H), 7.48 (d, 1H), 7.18 (d, 1H), 6.80 (d, 1H), 3.19 (s, 8H), 2.29 (s, 3H), 1.71 (s, 6H).

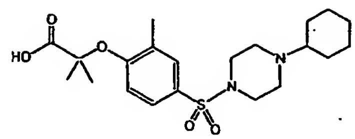
Example 24



2-{4-[4-(2-Methoxy-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.55 (s, 1H), 7.51 (d, 1H), 7.00

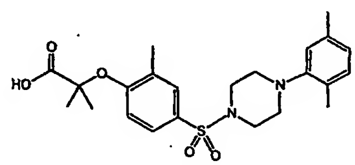
(m, 1H), 6.92 (d, 1H), 6.82 (d, 1H), 6.78 (d, 1H), 3.80 (s, 3H), 3.18 (s, 4H), 3.12 (s, 4H), 2.80 (s, 3H), 1.69 (s, 6H).

<u>Example 25</u>



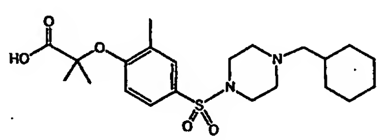
2-[4-(4-Cyclohexyl-piperazine-1-sulfonyl)-2-methyl-phenoxy]-2-methyl-propionic acid. [1]H NMR (400 MHz, $CDCl_3$) δ ppm. 7.50 (s, 1H), 7.41 (d, 1H), 6.76 (d, 1H), 3.21 (s, 4H), 3.02 (t, 4H), 2.25 (s, 3H), 2.08 (m, 2H), 1.88 (m, 4H), 1.58 (s, 6H), 1.25-1.37 (m, 4H).

<u>Example 26</u>



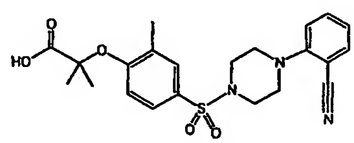
2-{4-[4-(2,5-Dimethyl-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. [1]H NMR (400 MHz, $CDCl_3$) δ ppm. 7.59 (s, 1H), 7.53 (d, 1H), 7.02 (d, 1H), 6.81 (m, 3H), 3.16 (s, board, 4H), 2.97 (t, 4H), 2.31 (s, 3H), 2.29 (s, 3H), 2.15 (s, 3H), 1.72 (s, 6H).

<u>Example 27</u>



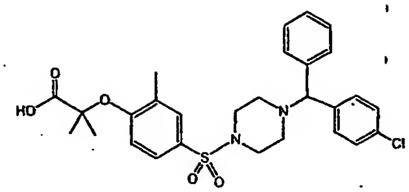
2-[4-(4-Cyclohexylmethyl-piperazine-1-sulfonyl)-2-methyl-phenoxy]-2-methyl-propionic acid. [1]H NMR (400 MHz, $CDCl_3$) δ ppm. 7.50 (s, 1H), 7.42 (d, 1H), 6.67 (d, 1H), 3.30 (s, 4H), 3.14 (s, 4H), 2.69 (d, 2H), 2.23 (s, 3H), 1.64-1.75 (m, 6H), 1.49 (s, 6H), 1.16 (m, 2H), 0.91 (m, 2H).

<u>Example 28</u>



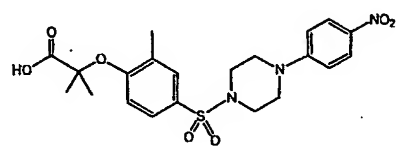
2-{4-[4-(2-Cyano-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. [1]H NMR (400 MHz, $CDCl_3$) δ ppm. 7.56 (s, 1H), 7.53 (m, 3H), 7.05 (t, 1H), 7.01 (d, 1H), 6.80 (d, 1H), 3.24 (s, board, 4H), 3.22 (s, 4H), 2.30 (s, 3H), 1.71 (s, 6H).

Example 29



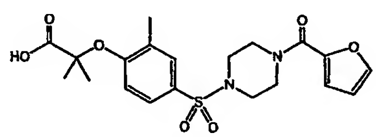
2-(4-{4-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.54 (s, 1H), 7.49 (d, 1H), 7.05 (m, 9H), 6.80 (d, 1H), 3.00 (s, 4H), 2.46 (s, board, 4H), 2.30 (s, 3H), 1.72 (s, 6H).

Example 30



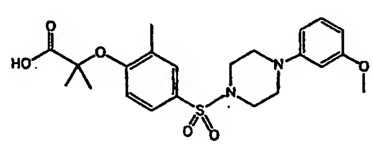
2-Methyl-2-{2-methyl-4-[4-(4-nitro-phenyl)-piperazine-1-sulfonyl)-phenoxy]-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 8.08 (d, 2H), 7.55 (s, 1H), 7.48 (d, 1H), 6.79 (d, 2H), 6.75 (d, 1H), 3.48 (t, 4H), 3.13 (t, 4H), 2.27 (s, 3H), 1.68 (s, 6H).

Example 31



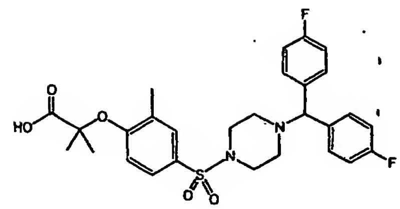
2-{4-[4-(Furan-2-carbonyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.50 (s, 1H), 7.45 (m, 2H), 7.03 (d, 1H), 6.75 (d, 1H), 6.45 (d, 1H), 3.89 (s, 4H), 3.05 (t, 4H), 2.26 (s, 3H), 1.67 (s, 6H).

Example 32



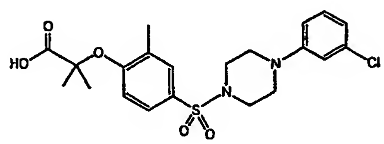
2-{4-[4-(3-Methoxy-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.55 (s, 1H), 7.50 (d, 1H), 7.15 (t, 1H), 6.76 (d, 1H), 6.48 (d, 1H), 6.46 (d, 1H), 6.42 (s, 1H), 3.76 (s, 3H), 3.21 (t, 4H), 3.13 (t, 4H), 2.27 (s, 3H), 1.67 (s, 6H).

Example 33



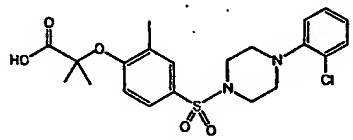
2-(4-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazine-1-sulfonyl}-2-methyl-phenoxy)-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.53 (s, 1H), 7.48 (d, 1H), 7.26 (m, 4H), 6.94 (d, 2H), 6.92 (d, 2H), 6.78 (d, 1H), 2.99 (s, 4H), 2.45 (s, board, 4H), 2.29 (s, 3H), 1.70 (s, 6H).

Example 34



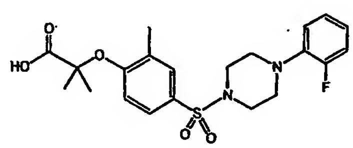
2-{4-[4-(3-Chloro-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.57 (s, 1H), 7.50 (d, 1H), 7.15 (t, 1H), 6.85 (d, 1H), 6.83 (s, 1H), 6.80 (d, 1H), 6.78 (d, 1H), 3.24 (t, 4H), 3.13 (t, 4H), 2.29 (s, 3H), 1.69 (s, 6H).

Example 35



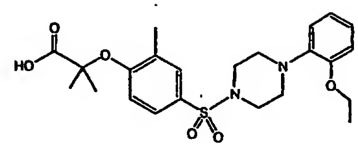
2-{4-[4-(2-Chloro-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.58 (s, 1H), 7.51 (d, 1H), 7.31 (d, 1H), 7.20 (d, 1H), 7.00 (t, 2H), 6.79 (d, 1H), 3.19 (s, 4H), 3.11 (t, 4H), 2.30 (s, 3H), 1.71 (s, 6H).

Example 36



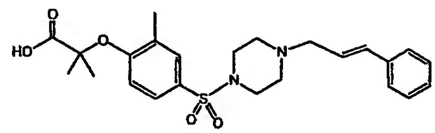
2-{4-[4-(2-Fluoro-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.57 (s, 1H), 7.51 (d, 1H), 7.04 (t, 1H), 6.95 (m, 3H), 6.79 (d, 1H), 3.17 (m, 8H), 2.29 (s, 3H), 1.70 (s, 6H).

Example 37



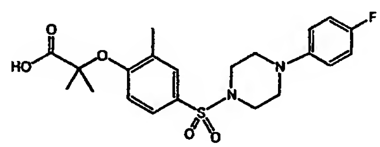
2-{4-[4-(2-Ethoxy-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.57 (s, 1H), 7.51 (d, 1H), 6.99 (t, 1H), 6.90 (d, 2H), 6.80 (t, 1H), 6.78 (d, 1H), 3.16 (m, 8H), 2.28 (s, 3H), 1.69 (s, 6H).

Example 38



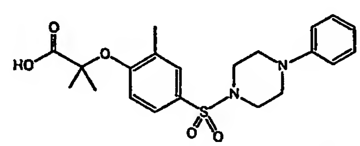
2-Methyl-2-{2-methyl-4-[4-(3-phenyl-allyl)-piperazine-1-sulfonyl)-phenoxy]-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.49 (s, 1H), 7.40 (d, 1H), 7.32 (m, 5H), 6.73 (d, 1H), 6.64 (d, 1H), 6.21 (m, 1H), 3.50 (d, 2H), 3.25 (s, 4H), 3.10 (s, 4H), 2.23 (s, 3H), 1.54 (s, 6H).

Example 39



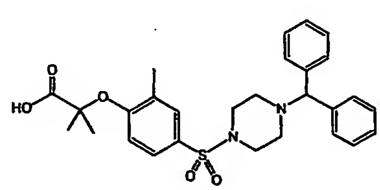
2-{4-[4-(4-Fluoro-phenyl)-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.56 (s, 1H), 7.50 (d, 1H), 6.96 (d, 1H), 6.92 (d, 1H), 6.84 (d, 1H), 6.83 (d, 1H), 6.77 (d, 1H), 3.15 (s, 8H), 2.28 (s, 3H), 1.68 (s, 6H).

Example 40



2-Methyl-2-[2-methyl-4-(4-phenyl-piperazine-1-sulfonyl)-phenoxy]-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.57 (s, 1H), 7.51 (d, 1H), 7.25 (t, 2H), 6.90 (m, 3H), 6.76 (d, 1H), 3.24 (s, 4H), 3.16 (s, 4H), 2.28 (s, 3H), 1.68 (s, 6H).

Example 41

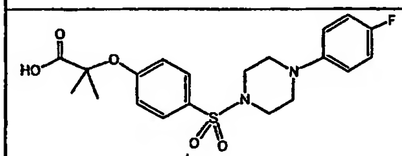
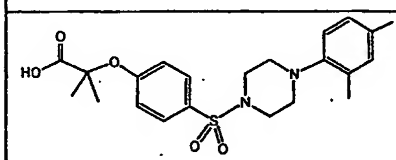
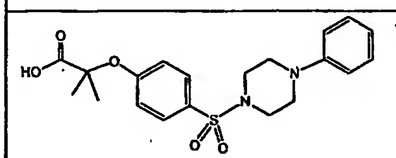
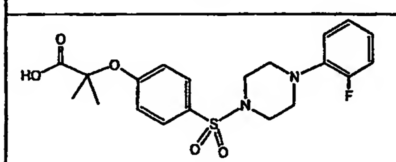
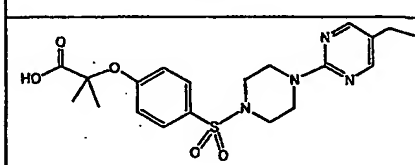
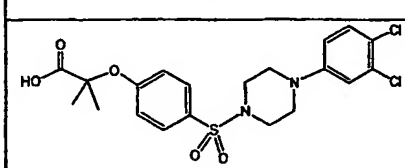


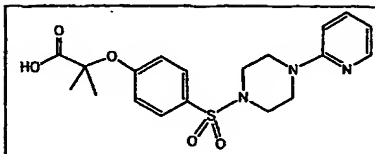
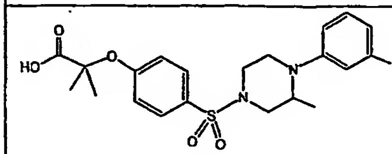
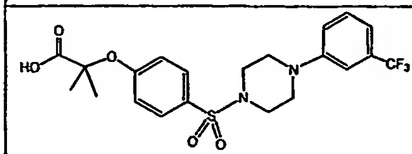
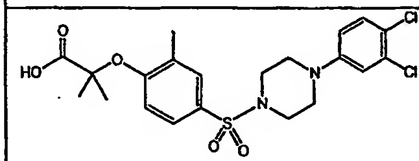
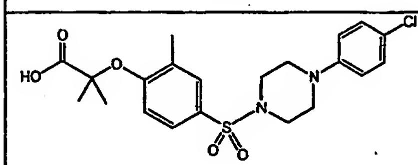
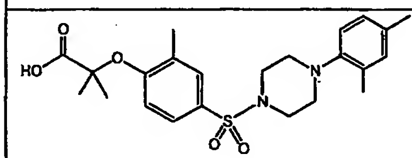
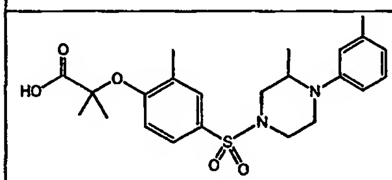
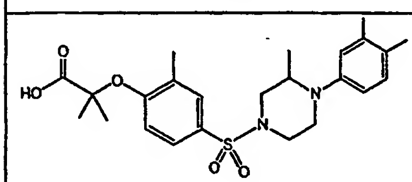
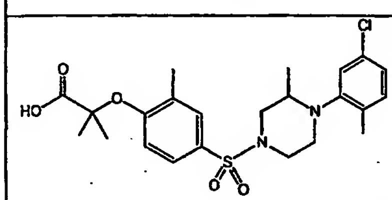
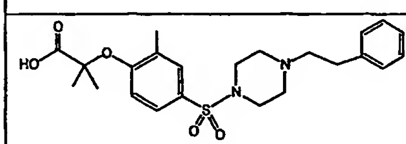
2-[4-(4-Benzhydryl-piperazine-1-sulfonyl]-2-methyl-phenoxy}-2-methyl-propionic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.53 (s, 1H), 7.45 (d, 1H), 7.34 (m, 4H), 7.21 (m, 4H), 7.17 (d, 2H), 6.80 (d, 1H), 3.02 (s, 4H), 2.51 (s, 4H), 2.29 (s, 3H), 1.69 (s, 6H).

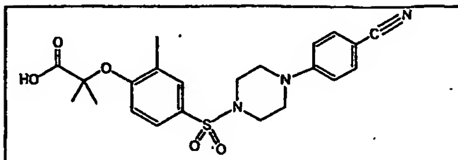
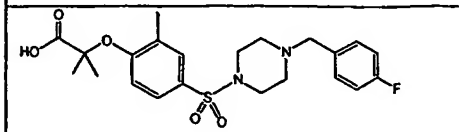
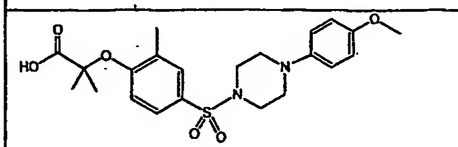
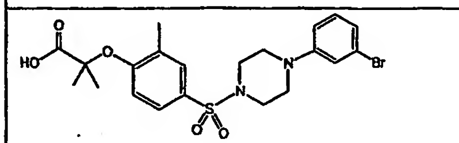
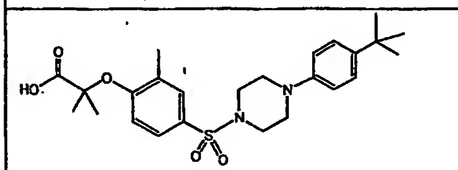
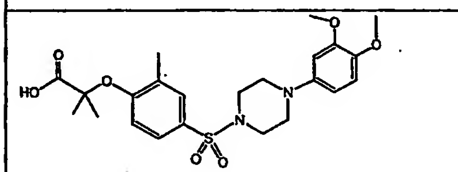
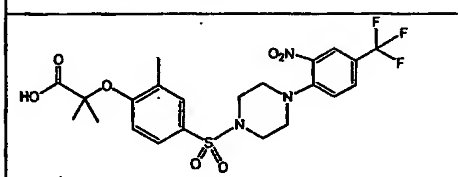
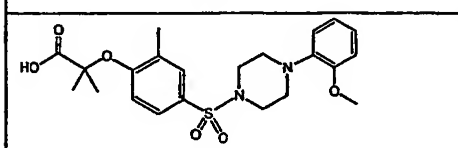
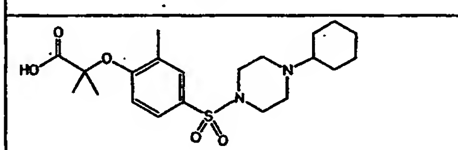
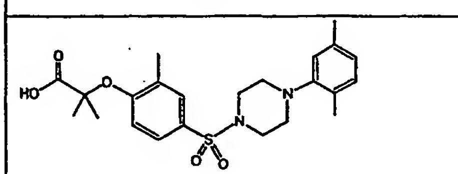
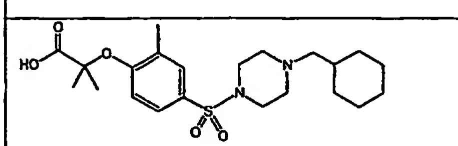
BIOLOGICAL ASSAYS OF THE COMPOUNDS OF THE INVENTION

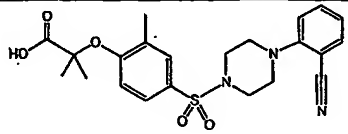
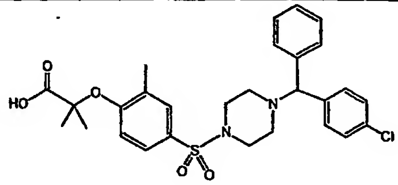
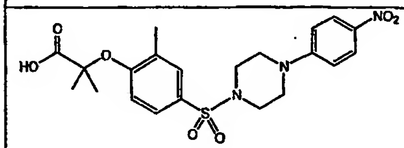
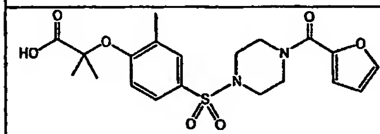
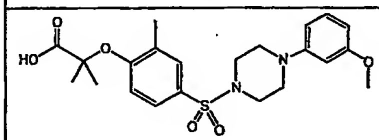
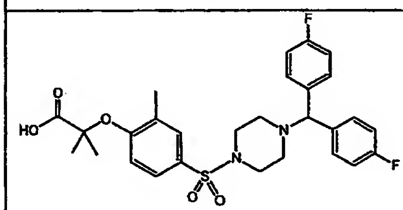
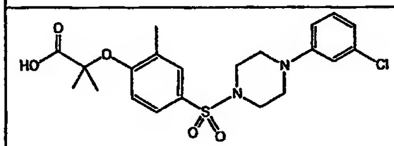
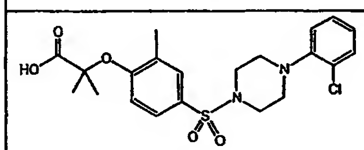
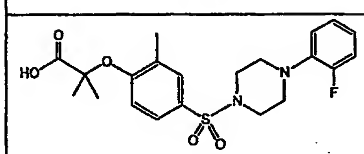
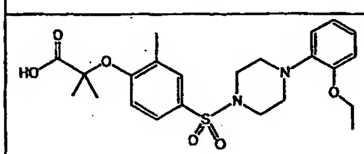
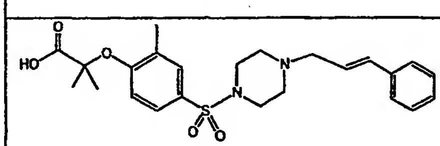
Compounds of Examples 1-41 were assayed to measure their biological activity with respect to their EC_{50} values and efficacy for modulating PPAR-alpha, PPAR-gamma, and PPAR-delta as set forth in Table 2.

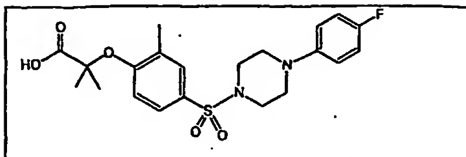
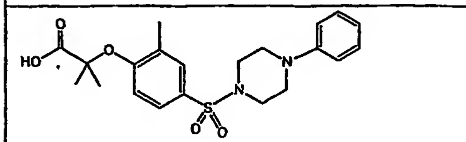
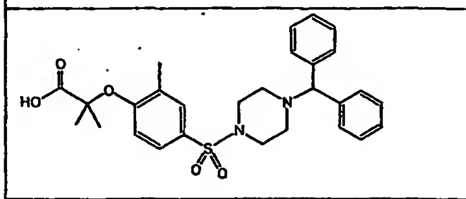
Table 2: Biological Activity

	EC_{50}		
COMPOUND	PPARα A >100μM B = 100-1 μM C < 1 μM	PPARδ A >100μM B = 100-1 μM C < 1 μM	PPARγ A >100μM B = 100-1 μM C < 1 μM
	A	B	A
	B	B	A
	A	B	A
	A	B	A
	B	B	B
	B	B	B

	A	A	A
	A	B	A
	A	B	B
	B	C	B
	A	C	B
	A	B	B
	A	C	B
	A	B	A
	A	B	A
	A	B	A

	A	B	A
	A	B	B
	A	B	B
	A	C	B
	A	B	B
	B	B	B
	A	B	B
	A	B	B
	A	B	A
	A	B	B
	A	B	B

	A	B	B
	B	B	B
	A	B	B
	A	B	A
	B	B	B
	B	B	B
	A	B	B
	A	B	B
	A	C	B
	B	B	B
	A	B	B

	A	C	B
	A	B	B
	A	B	B

It should be understood by a person of ordinary skill in the art that the foregoing examples illustrate embodiments of the invention but that the invention is not to be limited by the examples.

Examples of Pharmaceutical Formulations

As a guide only, the compounds of Formula (I) may be formulated into pharmaceutical compositions according to the following general examples.

Parenteral Composition

To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula (I) is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Oral Composition

To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula I is mixed with 750 mg of lactose. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

Those of skill in the art will appreciate that the compounds and uses disclosed herein can be used as PPAR modulators, providing a therapeutic effect.

One skilled in the art will appreciate that these methods and compounds are and may be adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods, procedures, and

compounds described herein are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the claims.

It will be apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Those skilled in the art recognize that the aspects and embodiments of the invention set forth herein may be practiced separate from each other or in conjunction with each other. Therefore, combinations of separate embodiments are within the scope of the invention as claimed herein.

All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

The invention illustratively described herein may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by certain embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting

of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described.

Other embodiments are within the following claims.